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(54) Title: PIPERIDINE GLYCINE TRANSPORTER INHIBITORS

(57) Abstract: The present invention is directed to piperidine compounds that inhibit the glycine transporter GlyT1 and which are useful in the treatment of neurological and psychiatric disorders associated with glycinergic or glutamatergic neurotransmission dysfunction and diseases in which the glycine transporter GlyT1 is involved.



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TITLE OF THE INVENTION

PIPERIDINE GLYCINE TRANSPORTER INHIBITORS

BACKGROUND OF THE INVENTION

5 Schizophrenia is a debilitating psychiatric disorder characterized by a combination of negative (blunted affect, withdrawal, anhedonia) and positive (paranoia, hallucinations, delusions) symptoms as well as marked cognitive deficits. While the etiology of schizophrenia is currently unknown, the disease appears to be produced by a complex interaction of biological, environmental, and genetic factors. Over 40 years ago it was found that phencyclidine (PCP) induces a psychotic state in humans that is very similar to that observed in schizophrenic patients. The finding that the main mode of action of PCP is that of a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) subtype of ionotropic glutamate receptor stimulated a series of studies that have led to the development of the NMDA receptor hypofunction model of schizophrenia (Jentsch JD and Roth RH, 1999 Neuropsychopharmacology, 20:201).

15 Fast glutamatergic transmission in the mammalian central nervous system is primarily mediated by the excitatory amino acid glutamate acting on ionotropic glutamate receptors (iGluRs). The iGluRs are comprised of three major subclasses, including the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and NMDA receptor subtypes (Hollmann M and Heinemann S, 1994, Annu. Rev. Neurosci. 17:31). These three subclasses are multimeric ligand-gated cation channels which open in response to glutamate binding to induce a depolarizing excitatory post synaptic current. Molecular cloning has revealed that the NMDA receptor family is composed of two primary subunits, NR1 and NR2. In addition a novel inhibitory subunit which is developmentally regulated termed NR3 has been recently described. A high degree of molecular diversity exists within each set of subunits. To date, only one NR1 subunit gene has been cloned; however, alternative splicing of the NR1 gene can produce eight different subunits. In contrast, 4 genes have been cloned for the NR2 subunit (NR2A, NR2B, NR2C, and NR2D), some of which exhibit alternative splicing (Hollmann M and Heinemann S, 1994, Annu. Rev. Neurosci. 17:31). These multiple subunits form heteromeric glutamate-gated ion channels. While the precise subunit stoichiometry of the naturally occurring receptor remains unknown, both the NR1 and NR2 subunits are required for the expression of functionally active receptor-channel complexes in mammalian expression systems. Activation of the NMDA receptor requires the binding of both glutamate and glycine (Johnson JW and Ascher P, 1987, Nature 325:529). Interestingly, the binding sites for these two co-agonists exist on separate subunits as determined by site-directed mutagenesis studies (Laube B, Hirai H, Sturgess M, Betz H and Kuhse J, 1997, Neuron 18:493). On the NR2A and NR2B subunits, a binding pocket for glutamate is formed by interactions between the N-

terminus of the receptor and the extracellular loops. Analogous experiments have placed the glycine binding site in a homologous region of the NR1 subunit (Kuryatov A, Laube B, Betz H and Kuhse J, 1994, *Neuron* 12:1291). Depending on the actual subunit composition, glutamate and glycine activate the NMDA receptor with EC50 values in the high nanomolar to low micromolar range. In addition, the pore of the NMDA receptor is impermeable to magnesium. Under normal resting conditions, extracellular magnesium can bind to a site within the pore and produce a magnesium block of the channel. This magnesium block imparts a strong voltage dependence to the channel which allows the NMDA receptor to act as a coincidence detector requiring the binding of glutamate, glycine, and the occurrence of postsynaptic depolarization before conducting current. Of particular interest is the finding that the psychotomimetic drugs MK-801, PCP, and ketamine all act as open channel blockers of the NMDA receptor-channel by binding to a site that overlaps with the magnesium binding site. It is apparent that the rich diversity of NMDA receptor subunits and regulatory sites provides for a complex assortment of physiologically and pharmacologically distinct heteromeric receptors making the NMDA receptor an ideal target for the design of novel therapeutic compounds.

The NMDA receptor plays a critical role in a variety of neurophysiological phenomena, including but not limited to synaptic plasticity, cognition, attention and memory (Bliss T and Collingridge W, 1993, *Nature* 361:31; Morris RGM et al., 1986, *Nature* 319:774). Psychotomimetic drugs constitute a wide class of drugs including psychomotor stimulants (cocaine, amphetamine), hallucinogens (LSD), and NMDA receptor antagonists (PCP, ketamine). Of these, only the NMDA receptor antagonists appear to elicit a robust induction of the positive, negative, and cognitive symptoms of schizophrenia. Controlled studies of ketamine-induced psychosis in human subjects, as well as observations of symptoms from patients abusing PCP as a recreational drug, have produced a convincing list of similarities between NMDA receptor antagonist-induced psychosis and schizophrenia (Jentsch JD and Roth RH, 1999 *Neuropsychopharmacology*, 20:201). NMDA-receptor antagonists faithfully mimic the symptoms of schizophrenia to the extent that it is difficult to differentiate the two in the clinic. In addition, NMDA receptor antagonists can exacerbate the symptoms in schizophrenics, and can trigger the re-emergence of symptoms in stable patients. Finally, the finding that NMDA receptor co-agonists such as glycine, D-cycloserine, and D-serine produce benefits in schizophrenic patients implicates NMDA receptor hypofunction in this disorder, and indicate that increasing NMDA receptor activation may provide a therapeutic benefit (Leiderman E et al., 1996, *Biol. Psychiatry* 39:213, Javitt DC et al., 1994, *Am. J. Psychiatry* 151:1234, Heresco-Levy U, 2000, *Int. J. Neuropsychopharmacol.* 3:243, Tsai G et al., 1998, *Biol. Psychiatry* 44:1081). A large number of studies in animal models lend support to the NMDA hypofunction hypothesis of schizophrenia. Recent generation of a mutant mouse expressing only 5% of normal levels of the NMDA NR1 subunit have shown that this decrease in functional NMDA receptors

induces a state very similar to that observed in other animal models of schizophrenia (Mohn AR et al., 1999, Cell 98:427). Besides schizophrenia, dysfunction of glutamatergic pathways has been implicated in a number of disease states in the human central nervous system (CNS) including but not limited to cognitive deficits, dementia, Parkinson disease, Alzheimer disease and bipolar disorder.

5 NMDA receptor function can be modulated by altering the availability of the co-agonist glycine. This approach has the critical advantage of maintaining activity-dependent activation of the NMDA receptor because an increase in the synaptic concentration of glycine will not produce an activation of NMDA receptors in the absence of glutamate. Since synaptic glutamate levels are tightly maintained by high affinity transport mechanisms, an increased activation of the glycine site will only
10 enhance the NMDA component of activated synapses. Clinical trials in which high doses of glycine were administered orally as an add-on to standard neuroleptic therapy showed an improvement of the symptoms of schizophrenia patients (Javitt et al. Int. J. Neuropsychopharmacol. (2001) 4: 385-391). One way to increase synaptic glycine levels without administering exogenous glycine is to inhibit its removal from the synapse. Evidence that this approach would be useful in treating schizophrenia comes from a
15 double-blind placebo controlled study in which sarcosine was administered to patients suffering from schizophrenia, but who were poorly responsive to antipsychotic drugs. A beneficial effect was observed on positive, negative and cognitive symptoms, indicating that inhibition of glycine re-uptake is a reasonable approach to the treatment of schizophrenia.

Two specific glycine transporters, GlyT1 and GlyT2 have been identified and shown to
20 belong to the Na^+/Cl^- dependent family of neurotransmitter transporters which includes taurine, γ -aminobutyric acid (GABA), proline, monoamines and orphan transporters (Smith KE et al., 1992, Neuron 8:927; Borowsky B et al., 1993, Neuron 10:851; Liu QR et al., 1993, J. Biol. Chem. 268:22802; Kim KM et al., 1994, Mol. Pharmacol. 45:608; Morrow JA et al., 1998, FEBS Lett. 439:334; Nelson N, 1998, J. Neurochem. 71:1785). GlyT1 and GlyT2 have been isolated from different species and shown to
25 have only 50% identity at the amino acid level. They also have a different pattern of expression in mammalian central nervous system with GlyT2 being expressed in spinal cord, brainstem and cerebellum and GlyT1 present in these regions as well as forebrain areas such as cortex, hippocampus, septum and thalamus (Smith KE et al., 1992, Neuron 8:927; Borowsky B et al., 1993, Neuron 10:851; Liu QR et al., 1993, J. Biol. Chem. 268:22802). At the cellular level, GlyT2 has been reported to be expressed by
30 glycinergic nerve endings in rat spinal cord whereas GlyT1 appears to be preferentially expressed by glial cells (Zafra F et al., 1995, J. Neurosci. 15:3952). These expression studies have led to the conclusion that GlyT2 is predominantly responsible for glycine uptake at glycinergic synapses whereas GlyT1 is involved in monitoring glycine concentration in the vicinity of NMDA receptor expressing synapses. Recent functional studies in rat have shown that blockade of GlyT1 with the potent inhibitor

(N-[3-(4'-fluorophenyl)-3-(4'-phenylphenoxy)propyl])sarcosine (NFPS) potentiates NMDA receptor activity and NMDA receptor-dependent long-term potentiation in rat (Bergeron R et al., 1998, PNAS USA 95:15730; Kinney G et al., 2003, J. Neurosci. 23:7586). Furthermore, NFPS has been reported to enhance pre-pulse inhibition in mice, a measure of sensory gating that is known to be deficient in schizophrenia patients (Kinney G et al., 2003, J. Neurosci. 23:7586). These physiological effects of GlyT1 in forebrain regions together with clinical reports showing the beneficial effects of GlyT1 inhibitor sarcosine in improving symptoms in schizophrenia patients (Tsai and Coyle WO99/52519) indicate that selective GlyT1 uptake inhibitors represent a new class of antipsychotic drugs.

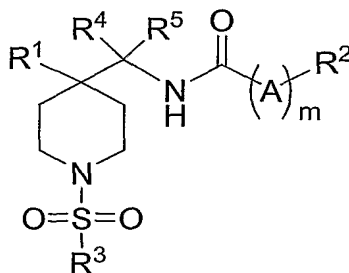
10 SUMMARY OF THE INVENTION

The present invention is directed to compounds that inhibit the glycine transporter GlyT1 and which are useful in the treatment of neurological and psychiatric disorders associated with glutamatergic neurotransmission dysfunction and diseases in which the glycine transporter GlyT1 is involved.

15

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of the formula I:



I

20 wherein:

R¹ is -(CH₂)_n-R^{1a}, wherein n is independently 0-6, and R^{1a} is selected from the group consisting of:

- (1) C₁-6alkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxy, phenyl substituted with R^{2a}, R^{2b} and R^{2c}, or heterocycle substituted with R^{2a}, R^{2b} and R^{2c},
- (2) C₃-6cycloalkyl, which is unsubstituted or substituted with C₁-6alkyl, 1-6 halogen, hydroxy or -NR¹⁰R¹¹,
- (3) piperidiny, which is unsubstituted or substituted with C₁-6alkyl, 1-6 halogen, hydroxy, -O-C₁-6alkyl, or -NR¹⁰R¹¹,
- (4) piperazinyl, which is unsubstituted or substituted with C₁-6alkyl, 1-6 halogen, hydroxy,

25

-O-C₁₋₆alkyl, or -NR¹⁰R¹¹,

- (5) tetrahydropyranyl or tetrahydrofuranyl, which is unsubstituted or substituted with C₁₋₆alkyl, 1-6 halogen, hydroxy, -O-C₁₋₆alkyl, or -NR¹⁰R¹¹,
- (6) morpholinyl, which is unsubstituted or substituted with C₁₋₆alkyl, 1-6 halogen, hydroxy, -O-C₁₋₆alkyl, or -NR¹⁰R¹¹,
- (7) -O-C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxy or -NR¹⁰R¹¹,
- (8) -CO₂R⁹,

wherein R⁹ is independently selected from:

- (a) hydrogen,
- (b) -C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 fluoro,
- (c) benzyl, and
- (d) phenyl,
- (9) -NR¹⁰R¹¹,

wherein R¹⁰ and R¹¹ are independently selected from:

- (a) hydrogen,
- (b) -C₁₋₆alkyl, which is unsubstituted or substituted with hydroxy, 1-6 fluoro or -NR¹²R¹³, where R¹² and R¹³ are independently selected from hydrogen and -C₁₋₆alkyl,
- (c) -C₃₋₆cycloalkyl, which is unsubstituted or substituted with hydroxy, 1-6 fluoro or -NR¹²R¹³,
- (d) benzyl,
- (e) phenyl, and
- (10) -CONR¹⁰R¹¹;

R² is selected from the group consisting of:

- (1) phenyl, which is substituted with R^{2a}, R^{2b} and R^{2c},
- (2) heterocycle, which is substituted with R^{2a}, R^{2b} and R^{2c},
- (3) C₁₋₈alkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxy, -NR¹⁰R¹¹, phenyl or heterocycle, where the phenyl or heterocycle is substituted with R^{2a}, R^{2b} and R^{2c},
- (4) C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxy or -NR¹⁰R¹¹, and

- (5) -C₁₋₆alkyl-(C₃₋₆cycloalkyl), which is unsubstituted or substituted with 1-6 halogen, hydroxy or -NR¹⁰R¹¹;

R^{2a}, R^{2b} and R^{2c} are independently selected from the group consisting of:

- 5 (1) hydrogen,
- (2) halogen,
- (3) -C₁₋₆alkyl, which is unsubstituted or substituted with:
 - (a) 1-6 halogen,
 - (b) phenyl,
 - 10 (c) C₃₋₆cycloalkyl, or
 - (d) -NR¹⁰R¹¹,
- (4) -O-C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halogen,
- (5) -O-phenyl,
- (6) hydroxy,
- 15 (7) -SCF₃,
- (8) -SCHF₂,
- (9) -SCH₃,
- (10) -CO₂R⁹,
- (11) -CN,
- 20 (12) -SO₂R⁹,
- (13) -SO₂-NR¹⁰R¹¹,
- (14) -NR¹⁰R¹¹,
- (15) -CONR¹⁰R¹¹, and
- (16) -NO₂;

25

R³ is selected from the group consisting of:

- (1) C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxyl, -NR¹⁰R¹¹,
- (2) C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxyl or -NR¹⁰R¹¹,
- 30 (3) -C₁₋₆alkyl-(C₃₋₆cycloalkyl), which is unsubstituted or substituted with 1-6 halogen, hydroxy or -NR¹⁰R¹¹, and
- (4) -NR¹⁰R¹¹;

with the proviso that if R¹ is -CH₂-cyclopropyl, then R³ is -NR¹⁰R¹¹ or

-C₁₋₆alkyl-(C₃₋₆cycloalkyl), which is unsubstituted or substituted with 1-6 halogen, hydroxy or -NR¹⁰R¹¹;

R⁴ and R⁵ are independently selected from the group consisting of:

- 5 (1) hydrogen, and
 (2) C₁₋₆alkyl, which is unsubstituted or substituted with halogen or hydroxyl,
 or R⁴ and R⁵ taken together form a C₃₋₆cycloalkyl ring;

A is selected from the group consisting of:

- 10 (1) -O-, and
 (2) -NR¹⁰-;

m is zero or one, whereby when m is zero, R² is attached directly to the carbonyl;
and pharmaceutically acceptable salts thereof.

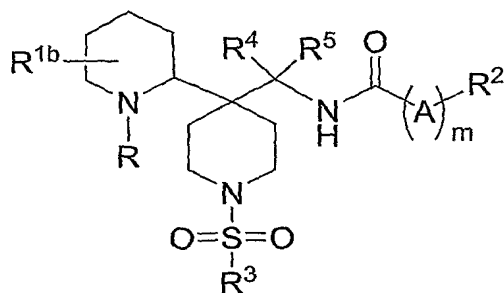
15 In an embodiment, the present invention includes compounds wherein R¹ is
-(CH₂)_n-R^{1a}, wherein n is independently 0-6, and R^{1a} is selected from the group consisting of:

- (1) C₃₋₆cycloalkyl, which is unsubstituted or substituted with C₁₋₆alkyl, 1-6 halogen, or
 hydroxy.
 (2) piperidinyl, which is unsubstituted or substituted with C₁₋₆alkyl, 1-6 halogen, hydroxy,
 or -O-C₁₋₆alkyl,
20 (3) piperazinyl, which is unsubstituted or substituted with C₁₋₆alkyl, 1-6 halogen, hydroxy,
 or -O-C₁₋₆alkyl,
 (4) tetrahydropyranyl, which is unsubstituted or substituted with C₁₋₆alkyl, 1-6 halogen,
 hydroxy, or -O-C₁₋₆alkyl, and
 (5) morpholinyl, which is unsubstituted or substituted with C₁₋₆alkyl, 1-6 halogen, hydroxy,
25 or -O-C₁₋₆alkyl.

Further within this embodiment, the present invention includes compounds wherein R¹
is selected from the group consisting of:

- (1) -CH₂-cyclopropyl,
 (2) piperidinyl,
30 (3) N-methyl-piperidinyl,
 (4) N-methyl-piperazinyl, and
 (5) morpholinyl.

An embodiment of the present invention includes compounds of the formula Ia:



Ia

wherein:

R is selected from the group consisting of:

- 5 (1) hydrogen, and
 (2) C₁-6alkyl;

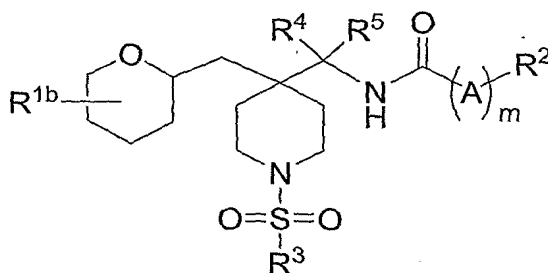
R^{1b} is selected from the group consisting of:

- 10 (1) hydrogen,
 (2) C₁-6alkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxyl or phenyl,
 (3) hydroxy ,
 (4) -O-C₁-6alkyl,
 (5) halogen, and
 (6) -NR¹⁰R¹¹;

and R², R³, R⁴, R⁵, A and m are defined herein;

- 15 or a pharmaceutically acceptable salt thereof.

An embodiment of the present invention includes compounds of the formula Ia':



Ia'

wherein:

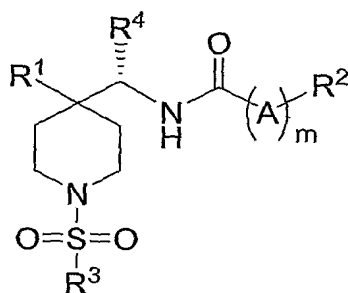
- 20 R^{1b} is selected from the group consisting of:

- (1) hydrogen,
 (2) C₁-6alkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxyl or phenyl,

- (3) hydroxy,
- (4) -O-C₁₋₆alkyl,
- (5) halogen, and
- (6) -NR¹⁰R¹¹;

5 and R², R³, R⁴, R⁵, A and m are defined herein;
or a pharmaceutically acceptable salt thereof.

An embodiment of the present invention includes compounds of the formula Ib:



Ib

10 wherein R⁴ is C₁₋₆alkyl, and R¹, R², R³, A and m are defined herein;
or a pharmaceutically acceptable salt thereof or an individual enantiomer or diastereomer thereof.

An embodiment of the present invention includes compounds wherein R⁴ is C₁₋₃alkyl and R⁵ is hydrogen or C₁₋₃alkyl.

15 Within this embodiment, the present invention includes compounds wherein R⁴ is C₁₋₃alkyl in the (S) configuration and R⁵ is hydrogen.

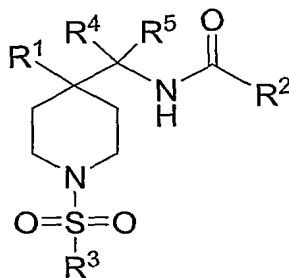
Also within this embodiment, the present invention includes compounds wherein R⁴ is methyl in the (S) configuration and R⁵ is hydrogen.

Also within this embodiment, the present invention includes compounds wherein R⁴ is methyl and R⁵ is methyl.

20 Also within this embodiment, the present invention includes compounds wherein R⁴ is hydrogen and R⁵ is hydrogen.

An embodiment of the present invention includes compounds wherein m is zero.

Within this embodiment, the present invention includes compounds of the formula Ic:



Ic

wherein R^1 , R^2 , R^3 , R^4 and R^5 are defined herein;
or a pharmaceutically acceptable salt thereof.

5 Further within this embodiment, the present invention includes compounds wherein R^2 is selected from the group consisting of:

- (1) phenyl, which is substituted with R^{2a} , R^{2b} and R^{2c} ,
- (2) thienyl, which is substituted with R^{2a} , R^{2b} and R^{2c} ,
- (3) C_{1-8} alkyl, which is unsubstituted or substituted with 1-6 halogen, phenyl or
- 10 $-NR^{10}R^{11}$, where the phenyl is substituted with R^{2a} , R^{2b} and R^{2c} ,
- (4) C_{3-6} cycloalkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxy or $-NR^{10}R^{11}$, and

R^{2a} , R^{2b} and R^{2c} are independently selected from the group consisting of:

- (1) hydrogen,
- 15 (2) halogen,
- (3) $-C_{1-6}$ alkyl,
- (4) $-O-C_{1-6}$ alkyl,
- (5) $-CF_3$,
- (6) $-OCF_3$,
- 20 (7) $-OCHF_2$,
- (8) $-SCF_3$,
- (9) $-SCHF_2$, and
- (10) $-NH_2$.

Also further within this embodiment, the present invention includes compounds wherein

25 R^2 is phenyl or thienyl and R^{2a} , R^{2b} and R^{2c} are independently selected from the group consisting of:

- (1) hydrogen,
- (2) halogen,
- (3) $-C_{1-6}$ alkyl,

- (4) -O-C₁₋₆alkyl,
 (5) -CF₃,
 (6) -OCF₃,
 (7) -OCHF₂,
 (8) -SCF₃,
 (9) -SCHF₂, and
 (10) -NH₂.

Also further within this embodiment, the present invention includes compounds wherein R² is phenyl and R^{2a}, R^{2b} and R^{2c} are independently selected from the group consisting of:

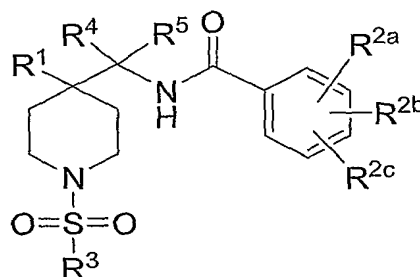
- (1) hydrogen,
 (2) fluoro,
 (3) chloro,
 (4) bromo,
 (5) -OCH₃,
 (6) -CF₃, and
 (7) -NH₂.

Also further within this embodiment, the present invention is directed to compounds wherein R² is phenyl and R^{2a}, R^{2b} and R^{2c} are independently selected from the group consisting of:

- (1) hydrogen,
 (2) fluoro,
 (3) chloro, and
 (4) bromo.

Also further within this embodiment, the present invention is directed to compounds wherein R² is 2,4-dichlorophenyl.

Within this embodiment the present invention includes compounds of the formula Id:

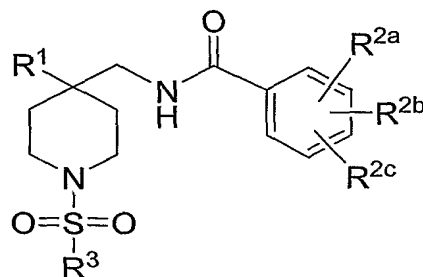


Id

wherein R¹, R^{2a}, R^{2b}, R^{2c}, R³, R⁴ and R⁵ are defined herein;

and pharmaceutically acceptable salts thereof.

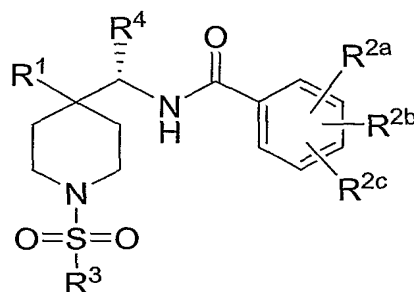
Within this embodiment, the present invention includes compounds of the formula Id'



Id'

- 5 wherein R¹, R^{2a}, R^{2b}, R^{2c} and R³ are defined herein;
and pharmaceutically acceptable salts thereof.

Also within this embodiment, the present invention includes compounds of the formula Id'':



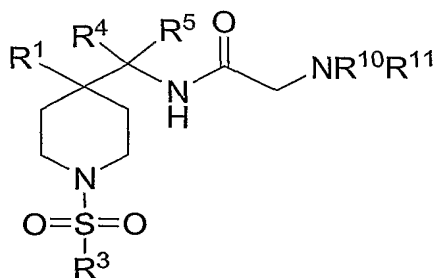
Id''

- 10 wherein R¹, R^{2a}, R^{2b}, R^{2c}, R³ and R⁴ are defined herein;
and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

An embodiment of the present invention includes compounds wherein wherein A is

-NR¹⁰-.

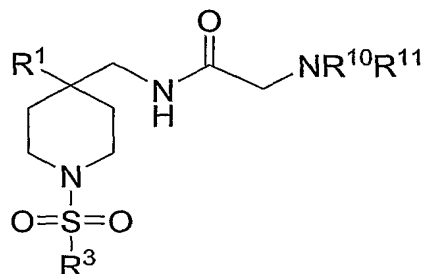
- 15 An embodiment of the present invention includes compounds of the formula If:



If

wherein R^1 , R^3 , R^4 , R^5 , R^{10} and R^{11} are defined herein;
or a pharmaceutically acceptable salt thereof.

Within this embodiment, the present invention includes compounds of the formula If:



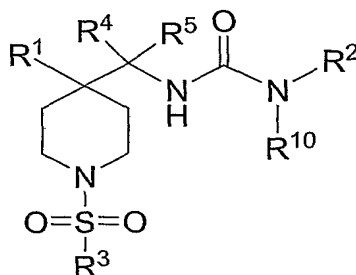
If'

wherein R^1 , R^3 , R^{10} and R^{11} are defined herein;
and pharmaceutically acceptable salts thereof.

An embodiment of the present invention includes compounds wherein wherein A is

-NR¹⁰-.

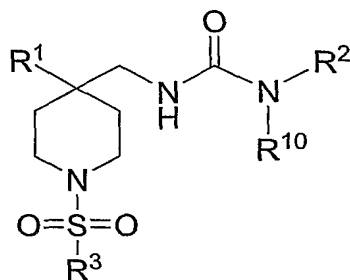
Within this embodiment, the present invention includes compounds of the formula Ig:



Ig

wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^{10} are defined herein;
or a pharmaceutically acceptable salt thereof.

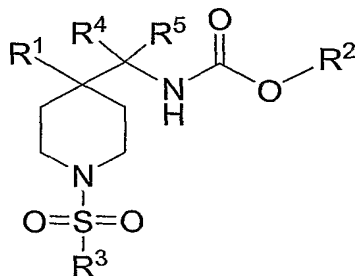
An embodiment of the present invention includes compounds of the formula Ig':



Ig'

wherein R¹, R², R³ and R¹⁰ are defined herein;
and pharmaceutically acceptable salts thereof.

- 5 An embodiment of the present invention includes compounds wherein A is -O-.
Within this embodiment, the present invention includes compounds of the formula Ih:



Ih

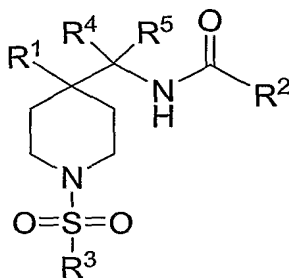
- wherein R¹, R², R³, R⁴ and R⁵ are defined herein;
10 or a pharmaceutically acceptable salt thereof.

An embodiment of the present invention includes compounds wherein R³ is -NH(C₁₋₆alkyl) or -N(C₁₋₆alkyl)₂. Within this embodiment, the present invention includes compounds wherein R³ is -NHCH₂CH₃ or -N(CH₃)₂.

- 15 An embodiment of the present invention includes compounds wherein R³ is C₁₋₆alkyl, which is unsubstituted or substituted with fluoro, C₃₋₆cycloalkyl, C₁₋₆alkyl-cyclopropyl, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)(C₁₋₆alkyl) or azediny, which is unsubstituted or substituted with fluoro.

- 20 Within this embodiment, the present invention includes compounds wherein R³ is -CH₂CH₃. Within this embodiment, the present invention includes compounds wherein R³ is -CH₂CH₂F. Within this embodiment, the present invention includes compounds wherein R³ is -(CH₂)₂CH₃. Within this embodiment, the present invention includes compounds wherein R³ is cyclopropyl. Within this embodiment, the present invention includes compounds wherein R³ is -CH₂cyclopropyl.

An embodiment of the present invention includes compounds of the formula Ij:



Ij

wherein:

5 R^1 is $-(CH_2)_n-R^{1a}$, wherein n is independently 0-6, and R^{1a} is selected from the group consisting of:

- (1) C_{1-6} alkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxy, or $-O-C_{1-6}$ alkyl,
- (2) tetrahydropyranyl, which is unsubstituted or substituted with C_{1-6} alkyl, 1-6 halogen, hydroxy, or $-O-C_{1-6}$ alkyl, and
- 10 (3) tetrahydrofuranyl, which is unsubstituted or substituted with C_{1-6} alkyl, 1-6 halogen, hydroxy, or $-O-C_{1-6}$ alkyl;

R^2 is selected from the group consisting of:

- (1) phenyl, which is substituted with R^{2a} , R^{2b} and R^{2c} ,
- (2) thienyl, which is substituted with R^{2a} , R^{2b} and R^{2c} ,
- 15 (3) C_{1-8} alkyl, which is unsubstituted or substituted with 1-6 halogen, or phenyl, where the phenyl is substituted with R^{2a} , R^{2b} and R^{2c} , and
- (4) C_{3-6} cycloalkyl, which is unsubstituted or substituted with 1-6 halogen or hydroxy;

R^{2a} , R^{2b} and R^{2c} are independently selected from the group consisting of:

- (1) hydrogen,
- 20 (2) halogen,
- (3) $-C_{1-6}$ alkyl,
- (4) $-O-C_{1-6}$ alkyl,
- (5) $-O$ -phenyl,
- (6) $-CF_3$,
- 25 (7) $-OCF_3$,
- (8) $-OCHF_2$,
- (9) $-CN$,
- (10) $-SCF_3$,

(11) $-\text{SCHF}_2$, and

(12) $-\text{NH}_2$;

R^3 is selected from the group consisting of:

(1) C_{1-6} alkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxyl,

$-\text{NR}^{10}\text{R}^{11}$,

wherein R^{10} and R^{11} are independently selected from:

(a) hydrogen,

(b) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with hydroxy, 1-6 fluoro or

$-\text{NR}^{12}\text{R}^{13}$, where R^{12} and R^{13} are independently selected from hydrogen and $-\text{C}_{1-6}$ alkyl,

(c) $-\text{C}_{3-6}$ cycloalkyl, which is unsubstituted or substituted with hydroxy, 1-6 fluoro or $-\text{NR}^{12}\text{R}^{13}$,

(d) benzyl,

(e) phenyl, and

(2) C_{3-6} cycloalkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxyl or $-\text{NR}^{10}\text{R}^{11}$,

(3) $-\text{C}_{1-6}$ alkyl- $(\text{C}_{3-6}$ cycloalkyl), which is unsubstituted or substituted with 1-6 halogen, hydroxy or $-\text{NR}^{10}\text{R}^{11}$, and

(4) $-\text{NR}^{10}\text{R}^{11}$;

R^4 and R^5 are independently selected from the group consisting of:

(1) hydrogen, and

(2) C_{1-6} alkyl, which is unsubstituted or substituted with halogen or hydroxyl, or R^4 and R^5 taken together form a C_{3-6} cycloalkyl ring;

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

An embodiment of the present invention includes compounds wherein R^1 is other than tetrahydropyranyl.

An embodiment of the present invention includes compounds wherein R^1 is other than 2-tetrahydropyranyl which is substituted with R^{1b} .

An embodiment of the present invention includes compounds wherein R^1 is other than tetrahydrofuranlyl.

An embodiment of the present invention includes compounds wherein R^1 is $-(\text{CH}_2)_n-\text{R}^{1a}$, wherein n is independently 0-6, and R^{1a} is C_{1-6} alkyl, which is unsubstituted or substituted with 1-6 halogen or hydroxy.

Further within this embodiment, the present invention includes compounds wherein R^1 is C_{1-6} alkyl which is unsubstituted.

Further within this embodiment, the present invention includes compounds wherein R^1 is selected from the group consisting of:

- 5 (1) methyl,
- (2) ethyl,
- (3) n-propyl,
- (4) isopropyl,
- (5) n-butyl,
- 10 (6) isobutyl,
- (7) sec-butyl,
- (8) tert-butyl,
- (9) n-pentyl,
- (10) isopentyl,
- 15 (11) neo-pentyl,
- (12) tert-pentyl, and
- (13) isohexyl.

Further within this embodiment, the present invention includes compounds wherein R^1 is selected from the group consisting of:

- 20 (1) isopropyl,
- (2) isobutyl, and
- (3) isopentyl.

Further within this embodiment, the present invention includes compounds wherein R^1 is isobutyl.

25 An embodiment of the present invention includes compounds wherein R^1 is $-(CH_2)_n-R^{1a}$, wherein n is independently 1-5, and R^{1a} is selected from the group consisting of:

- (1) tetrahydropyranyl, which is unsubstituted or substituted with C_{1-6} alkyl, 1-6 halogen, hydroxy, or $-O-C_{1-6}$ alkyl, and
- (2) tetrahydrofuranyl, which is unsubstituted or substituted with C_{1-6} alkyl, 1-6 halogen, hydroxy, or $-O-C_{1-6}$ alkyl.
- 30

Further within this embodiment, the present invention includes compounds wherein R^1 is $-(CH_2)-R^{1a}$, and R^{1a} is selected from the group consisting of:

- (1) tetrahydropyranyl, which is unsubstituted or substituted with C_{1-6} alkyl, 1-6 halogen, or hydroxy, and

- (2) tetrahydrofuranyl, which is unsubstituted or substituted with C₁₋₆alkyl, 1-6 halogen, or hydroxyl.

Further within this embodiment, the present invention includes compounds wherein R¹ is -(CH₂)-R^{1a}, and R^{1a} is selected from the group consisting of:

- (1) 4-tetrahydropyranyl, which is unsubstituted or substituted with C₁₋₆alkyl, 1-6 halogen, or hydroxy, and
- (2) 2-tetrahydrofuranyl, which is unsubstituted or substituted with C₁₋₆alkyl, 1-6 halogen, or hydroxyl.

Further within this embodiment, the present invention includes compounds wherein R¹ is -(CH₂)-4-tetrahydropyranyl.

Further within this embodiment, the present invention includes compounds wherein R¹ is -(CH₂)-2-tetrahydrofuranyl.

An embodiment of the present invention includes compounds wherein R² is selected from the group consisting of:

- (1) phenyl, which is substituted with R^{2a}, R^{2b} and R^{2c},
- (2) C₁₋₈alkyl, which is unsubstituted or substituted with 1-6 halogen, phenyl or -NR¹⁰R¹¹, where the phenyl is substituted with R^{2a}, R^{2b} and R^{2c},
- (3) C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxy or -NR¹⁰R¹¹, and

R^{2a}, R^{2b} and R^{2c} are independently selected from the group consisting of:

- (1) hydrogen,
- (2) halogen,
- (3) -C₁₋₆alkyl,
- (4) -O-C₁₋₆alkyl,
- (5) -O-phenyl,
- (6) -CF₃,
- (7) -OCF₃,
- (8) -OCHF₂,
- (9) -CN,
- (10) -SCF₃,
- (11) -SCHF₂, and
- (12) -NH₂.

Also further within this embodiment, the present invention includes compounds wherein R² is phenyl and R^{2a}, R^{2b} and R^{2c} are independently selected from the group consisting of:

- (1) hydrogen,
(2) halogen,
(3) -C₁₋₆alkyl,
(4) -O-C₁₋₆alkyl,
5 (5) -O-phenyl,
(6) -CF₃,
(7) -OCF₃,
(8) -OCHF₂,
(9) -CN,
10 (10) -SCF₃,
(11) -SCHF₂, and
(12) -NH₂.

Also further within this embodiment, the present invention includes compounds wherein R² is phenyl and R^{2a}, R^{2b} and R^{2c} are independently selected from the group consisting of:

- 15 (1) hydrogen,
(2) fluoro,
(3) chloro,
(4) bromo,
(5) -OCH₃,
20 (6) -O-phenyl,
(7) -CF₃,
(8) -CH₃,
(9) -CN, and
(10) -NH₂.

25 Also further within this embodiment, the present invention is directed to compounds wherein R² is phenyl and R^{2a}, R^{2b} and R^{2c} are independently selected from the group consisting of:

- 30 (1) hydrogen,
(2) fluoro,
(3) chloro,
(4) bromo,
(5) -CF₃,
(6) -CN, and
(7) -CH₃.

Also further within this embodiment, the present invention is directed to compounds wherein R² independently selected from the group consisting of:

- (1) 2-bromophenyl,
- (2) 2-bromo-4-methylphenyl,
- 5 (3) 2-bromo-5-methylphenyl,
- (4) 2-bromo-6-methylphenyl,
- (5) 2-chlorophenyl,
- (6) 2-chloro-3,6-difluorophenyl,
- (7) 2-chloro-(4-trifluoromethyl)phenyl,
- 10 (8) 4-chloro-(2-trifluoromethyl)phenyl,
- (9) 2,3-dichlorophenyl,
- (10) 2,4-dichlorophenyl,
- (11) 2,4-difluorophenyl,
- (12) 2,4-dichloro-3-fluorophenyl,
- 15 (13) 2,4-dimethylphenyl,
- (14) 2-fluoro-(4-trifluoromethyl)phenyl,
- (15) 2,4-bis(trifluoromethyl)phenyl,
- (16) 2-methylphenyl, and
- (17) (4-trifluoromethyl)phenyl.

Also further within this embodiment, the present invention is directed to compounds wherein R² independently selected from the group consisting of:

- (1) 2-chloro-3,6-difluorophenyl,
- (2) 2-chloro-(4-trifluoromethyl)phenyl,
- (3) 4-chloro-(2-trifluoromethyl)phenyl,
- 25 (4) 2,3-dichlorophenyl,
- (5) 2,4-dichlorophenyl,
- (6) 2,4-difluorophenyl,
- (7) 2,4-dichloro-3-fluorophenyl,
- (8) 2-fluoro-(4-trifluoromethyl)phenyl, and
- 30 (9) 2,4-bis(trifluoromethyl)phenyl.

Also further within this embodiment, the present invention is directed to compounds wherein R² independently selected from the group consisting of:

- (1) 2-chloro-(4-trifluoromethyl)phenyl, and
- (2) 2,4-dichlorophenyl.

An embodiment of the present invention includes compounds wherein R^3 is C_{1-6} alkyl, which is unsubstituted or substituted with fluoro, C_{3-6} cycloalkyl, C_{1-6} alkyl-cyclopropyl, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)(C_{1-6} alkyl) or azediny, which is unsubstituted or substituted with fluoro.

Within this embodiment, the present invention includes compounds wherein R^3 is $-CH_2CH_3$. Within this embodiment, the present invention includes compounds wherein R^3 is $-CH_2CH_2F$. Within this embodiment, the present invention includes compounds wherein R^3 is $-(CH_2)_2CH_3$. Within this embodiment, the present invention includes compounds wherein R^3 is cyclopropyl. Within this embodiment, the present invention includes compounds wherein R^3 is $-CH_2$ cyclopropyl.

An embodiment of the present invention includes compounds wherein R^4 is hydrogen and R^5 is hydrogen.

An embodiment of the present invention includes compounds wherein R^4 is C_{1-3} alkyl and R^5 is hydrogen or C_{1-3} alkyl.

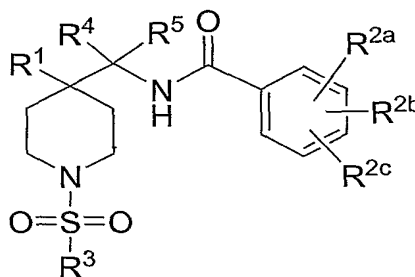
Within this embodiment, the present invention includes compounds wherein R^4 is C_{1-3} alkyl in the (S) configuration and R^5 is hydrogen.

Also within this embodiment, the present invention includes compounds wherein R^4 is methyl in the (S) configuration and R^5 is hydrogen.

Also within this embodiment, the present invention includes compounds wherein R^4 is methyl and R^5 is methyl.

An embodiment of the present invention includes compounds wherein n is 0, 1 or 2. within this embodiment, the present invention includes compounds wherein n is 0 or 1.

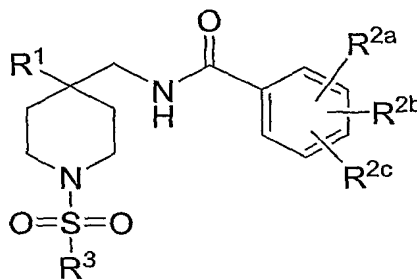
An embodiment of the present invention includes compounds of the formula Ik:



Ik

wherein R^1 , R^{2a} , R^{2b} , R^{2c} , R^3 , R^4 and R^5 are defined herein; and pharmaceutically acceptable salts thereof.

An embodiment of the present invention includes compounds of the formula Im:



Im

wherein R¹, R^{2a}, R^{2b}, R^{2c} and R³ are defined herein;
and pharmaceutically acceptable salts thereof.

Specific embodiments of the present invention include a compound which is selected from the group consisting of the subject compounds of the Examples herein and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

The compounds of the present invention may contain one or more chiral centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds. Formula I shows the structure of the class of compounds without preferred stereochemistry.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds

can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

As appreciated by those of skill in the art, halo or halogen as used herein are intended to include fluoro, chloro, bromo and iodo. Similarly, C₁₋₆, as in C₁₋₆alkyl is defined to identify the group as having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement, such that C₁₋₈alkyl specifically includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, hexyl, heptyl and octyl. A group which is designated as being independently substituted with substituents may be independently substituted with multiple numbers of such substituents. The term "heterocycle" as used herein includes both unsaturated and saturated heterocyclic moieties, wherein the unsaturated heterocyclic moieties (i.e. "heteroaryl") include benzoimidazolyl, benzimidazolonyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolaziny, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, and N-oxides thereof, and wherein the saturated heterocyclic moieties include azetidiny, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, thiomorpholinyl, and tetrahydrothienyl, and N-oxides thereof.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylamino-ethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like. When

the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids. It will be understood that, as used herein, references to the compounds of the present invention are meant to also include the pharmaceutically acceptable salts.

Exemplifying the invention is the use of the compounds disclosed in the Examples and herein. Specific compounds within the present invention include a compound which selected from the group consisting of the compounds disclosed in the following Examples and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

The subject compounds are useful in a method of inhibiting the glycine transporter GlyT1 activity in a patient such as a mammal in need of such inhibition comprising the administration of an effective amount of the compound. The present invention is directed to the use of the compounds disclosed herein as inhibitors of the glycine transporter GlyT1 activity. In addition to primates, especially humans, a variety of other mammals can be treated according to the method of the present invention.

The present invention is further directed to a method for the manufacture of a medicament for inhibiting glycine transporter GlyT1 activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The subject treated in the present methods is generally a mammal, preferably a human being, male or female, in whom inhibition of glycine transporter GlyT1 activity is desired. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. It is recognized that one skilled in the art may affect the neurological and psychiatric disorders by treating a patient presently afflicted with the disorders or by prophylactically treating a patient afflicted with such disorders with an effective amount of the compound of the present invention. As used herein, the terms "treatment" and "treating" refer to all processes wherein there may be a slowing, interrupting, arresting, controlling, or stopping of the progression of the neurological and psychiatric disorders described herein, but does not necessarily indicate a total elimination of all disorder symptoms, as well as the prophylactic therapy to retard the progression or reduce the risk of the noted conditions, particularly in a patient who is predisposed to such disease or disorder.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

The utility of the compounds in accordance with the present invention as inhibiting the glycine transporter activity, in particular GlyT1 activity, may be demonstrated by methodology known in the art. Human placental choriocarcinoma cells (JAR cells (ATCC No. HTB-144)) endogenously expressing GlyT1 were cultured in 96-well Cytostar scintillating microplates (Amersham Biosciences) in RPMI 1640 medium containing 10% fetal calf serum in the presence of penicillin (100 micrograms/milliliter) and streptomycin (100 micrograms/ milliliter). Cells were grown at 37°C in a humidified atmosphere of 5% CO₂ for 40-48 hours before the assay. Culture medium was removed from the Cytostar plate, and JAR cells were incubated with 30 microliters of TB1A buffer (120 mM NaCl, 2 mM KCl, 1 mM CaCl₂, 1 mM MgCl₂, 10 mM HEPES, 5 mM L-alanine, pH 7.5 adjusted with Tris base) with or without the compounds of the present invention for 1 minute. Then 30 microliters of [¹⁴C]-glycine diluted with TB1A was added to each well to give a final concentration of 10 micromolar. After incubation at room temperature for 3 hours, the Cytostar scintillating microplates were sealed and counted on a Top Count scintillation counter (Packard). Non-specific uptake of [¹⁴C]-glycine was determined in the presence of 10 mM unlabeled glycine. [¹⁴C]taurine uptake experiments were performed according to the same protocol except that 10 mM unlabeled taurine was used to determine non-specific uptake. To determine potencies, a range of concentrations of the compounds of the present invention was added to the cells, followed by the fixed concentration of [¹⁴C]glycine. The concentration of the present compound that inhibited half of the specific uptake of [¹⁴C]glycine (IC₅₀ value) was determined from the assay data by non-linear curve fitting.

In particular, the compounds of the following examples had activity in inhibiting specific uptake of [^{14}C]glycine in the aforementioned assay, generally with an IC_{50} value of less than about 10 micromolar. Preferred compounds within the present invention had activity in inhibiting specific uptake of [^{14}C]glycine in the aforementioned assay with an IC_{50} value of less than about 1 micromolar. These compounds were selective for [^{14}C]glycine uptake (by GlyT1 in the JAR cells) compared to [^{14}C]taurine uptake (by the taurine transporter TauT in the JAR cells). Such a result is indicative of the intrinsic activity of the compounds in use as inhibitors of GlyT1 transporter activity.

The NMDA receptor is central to a wide range of CNS processes, and plays a role in a variety of disease states in humans or other species. The action of GlyT1 transporters affects the local concentration of glycine around NMDA receptors. Selective GlyT1 inhibitors slow the removal of glycine from the synapse, causing the level of synaptic glycine to rise. This in turn increases the occupancy of the glycine binding site on the NMDA receptor, which increases activation of the NMDA receptor following glutamate release from the presynaptic terminal. Because a certain amount of glycine is needed for the efficient functioning of NMDA receptors, any change to that local concentration can affect NMDA-mediated neurotransmission. Changes in NMDA-mediated neurotransmission have been implicated in certain neuropsychiatric disorders such as dementia, depression and psychoses, for example schizophrenia, and learning and memory disorders, for example attention deficit disorders and autism.

The compounds of the present invention have utility in treating a variety of neurological and psychiatric disorders associated with glutamatergic neurotransmission dysfunction, including one or more of the following conditions or diseases: schizophrenia or psychosis including schizophrenia (paranoid, disorganized, catatonic or undifferentiated), schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition and substance-induced or drug-induced (phencyclidine, ketamine and other dissociative anaesthetics, amphetamine and other psychostimulants and cocaine) psychosis, psychotic disorder, psychosis associated with affective disorders, brief reactive psychosis, schizoaffective psychosis, "schizophrenia-spectrum" disorders such as schizoid or schizotypal personality disorders, or illness associated with psychosis (such as major depression, manic depressive (bipolar) disorder, Alzheimer's disease and post-traumatic stress syndrome), including both the positive and the negative symptoms of schizophrenia and other psychoses; cognitive disorders including dementia (associated with Alzheimer's disease, ischemia, multi-infarct dementia, trauma, vascular problems or stroke, HIV disease, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jacob disease, perinatal hypoxia, other general medical conditions or substance abuse); delirium, amnestic disorders or age related cognitive decline; anxiety disorders including acute stress disorder, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic attack, panic disorder, post-traumatic stress

disorder, separation anxiety disorder, social phobia, specific phobia, substance-induced anxiety disorder and anxiety due to a general medical condition; substance-related disorders and addictive behaviors (including substance-induced delirium, persisting dementia, persisting amnesic disorder, psychotic disorder or anxiety disorder; tolerance, dependence or withdrawal from substances including alcohol, amphetamines, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine, sedatives, hypnotics or anxiolytics); obesity, bulimia nervosa and compulsive eating disorders; bipolar disorders, mood disorders including depressive disorders; depression including unipolar depression, seasonal depression and post-partum depression, premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PDD), mood disorders due to a general medical condition, and substance-induced mood disorders; learning disorders, pervasive developmental disorder including autistic disorder, attention disorders including attention-deficit hyperactivity disorder (ADHD) and conduct disorder; NMDA receptor-related disorders such as autism, depression, benign forgetfulness, childhood learning disorders and closed head injury; movement disorders, including akinesias and akinetic-rigid syndromes (including Parkinson's disease, drug-induced parkinsonism, postencephalitic parkinsonism, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, parkinsonism-ALS dementia complex and basal ganglia calcification), medication-induced parkinsonism (such as neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremor), Gilles de la Tourette's syndrome, epilepsy, muscular spasms and disorders associated with muscular spasticity or weakness including tremors; dyskinesias [including tremor (such as rest tremor, postural tremor and intention tremor), chorea (such as Sydenham's chorea, Huntington's disease, benign hereditary chorea, neuroacanthocytosis, symptomatic chorea, drug-induced chorea and hemiballism), myoclonus (including generalised myoclonus and focal myoclonus), tics (including simple tics, complex tics and symptomatic tics), and dystonia (including generalised dystonia such as idiopathic dystonia, drug-induced dystonia, symptomatic dystonia and paroxysmal dystonia, and focal dystonia such as blepharospasm, oromandibular dystonia, spasmodic dysphonia, spasmodic torticollis, axial dystonia, dystonic writer's cramp and hemiplegic dystonia)]; urinary incontinence; neuronal damage including ocular damage, retinopathy or macular degeneration of the eye, tinnitus, hearing impairment and loss, and brain edema; emesis; and sleep disorders including insomnia and narcolepsy.

Of the disorders above, the treatment of schizophrenia, bipolar disorder, depression including unipolar depression, seasonal depression and post-partum depression, premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PDD), learning disorders, pervasive developmental disorder including autistic disorder, attention disorders including Attention-Deficit/Hyperactivity Disorder, autism, tic disorders including Tourette's disorder, anxiety disorders including phobia and post traumatic

stress disorder, cognitive disorders associated with dementia, AIDS dementia, Alzheimer's, Parkinson's, Huntington's disease, spasticity, myoclonus, muscle spasm, tinnitus and hearing impairment and loss are of particular importance.

In a specific embodiment, the present invention provides a method for treating cognitive disorders, comprising: administering to a patient in need thereof an effective amount of a compound of the present invention. Particular cognitive disorders are dementia, delirium, amnesic disorders and age-related cognitive decline. At present, the text revision of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (2000, American Psychiatric Association, Washington DC) provides a diagnostic tool that includes cognitive disorders including dementia, delirium, amnesic disorders and age-related cognitive decline. As used herein, the term "cognitive disorders" includes treatment of those mental disorders as described in DSM-IV-TR. The skilled artisan will recognize that there are alternative nomenclatures, nosologies and classification systems for mental disorders, and that these systems evolve with medical and scientific progress. Thus the term "cognitive disorders" is intended to include like disorders that are described in other diagnostic sources.

In another specific embodiment, the present invention provides a method for treating anxiety disorders, comprising: administering to a patient in need thereof an effective amount of a compound of the present invention. Particular anxiety disorders are generalized anxiety disorder, obsessive-compulsive disorder and panic attack. At present, the text revision of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (2000, American Psychiatric Association, Washington DC) provides a diagnostic tool that includes anxiety disorders are generalized anxiety disorder, obsessive-compulsive disorder and panic attack. As used herein, the term "anxiety disorders" includes treatment of those mental disorders as described in DSM-IV-TR. The skilled artisan will recognize that there are alternative nomenclatures, nosologies and classification systems for mental disorders, and that these systems evolve with medical and scientific progress. Thus the term "anxiety disorders" is intended to include like disorders that are described in other diagnostic sources.

In another specific embodiment, the present invention provides a method for treating schizophrenia or psychosis comprising: administering to a patient in need thereof an effective amount of a compound of the present invention. Particular schizophrenia or psychosis pathologies are paranoid, disorganized, catatonic or undifferentiated schizophrenia and substance-induced psychotic disorder. At present, the text revision of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (2000, American Psychiatric Association, Washington DC) provides a diagnostic tool that includes paranoid, disorganized, catatonic or undifferentiated schizophrenia and substance-induced psychotic disorder. As used herein, the term "schizophrenia or psychosis" includes treatment of those mental disorders as described in DSM-IV-TR. The skilled artisan will recognize that

there are alternative nomenclatures, nosologies and classification systems for mental disorders, and that these systems evolve with medical and scientific progress. Thus the term “schizophrenia or psychosis” is intended to include like disorders that are described in other diagnostic sources.

5 In another specific embodiment, the present invention provides a method for treating substance-related disorders and addictive behaviors, comprising: administering to a patient in need thereof an effective amount of a compound of the present invention. Particular substance-related disorders and addictive behaviors are persisting dementia, persisting amnestic disorder, psychotic disorder or anxiety disorder induced by substance abuse; and tolerance of, dependence on or withdrawal from substances of abuse. At present, the text revision of the fourth edition of the Diagnostic and
10 Statistical Manual of Mental Disorders (DSM-IV-TR) (2000, American Psychiatric Association, Washington DC) provides a diagnostic tool that includes persisting dementia, persisting amnestic disorder, psychotic disorder or anxiety disorder induced by substance abuse; and tolerance of, dependence on or withdrawal from substances of abuse. As used herein, the term “substance-related disorders and addictive behaviors” includes treatment of those mental disorders as described in DSM-IV-
15 TR. The skilled artisan will recognize that there are alternative nomenclatures, nosologies and classification systems for mental disorders, and that these systems evolve with medical and scientific progress. Thus the term “substance-related disorders and addictive behaviors” is intended to include like disorders that are described in other diagnostic sources.

20 In another specific embodiment, the present invention provides a method for treating pain, comprising: administering to a patient in need thereof an effective amount of a compound of the present invention. Particular pain embodiments are bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia), perioperative pain (general surgery, gynecological), chronic pain and neuropathic pain.

25 In another specific embodiment, the present invention provides a method for treating obesity or eating disorders associated with excessive food intake and complications associated therewith, comprising: administering to a patient in need thereof an effective amount of a compound of the present invention. At present, obesity is included in the tenth edition of the International Classification of Diseases and Related Health Problems (ICD-10) (1992 World Health Organization) as a general medical condition. The text revision of the fourth edition of the Diagnostic and Statistical Manual of Mental
30 Disorders (DSM-IV-TR) (2000, American Psychiatric Association, Washington DC) provides a diagnostic tool that includes obesity in the presence of psychological factors affecting medical condition. As used herein, the term “obesity or eating disorders associated with excessive food intake” includes treatment of those medical conditions and disorders described in ICD-10 and DSM-IV-TR. The skilled artisan will recognize that there are alternative nomenclatures, nosologies and classification systems for

general medical conditions, and that these systems evolve with medical and scientific progress. Thus the term "obesity or eating disorders associated with excessive food intake" is intended to include like conditions and disorders that are described in other diagnostic sources.

The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions noted herein.

The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the aforementioned diseases, disorders and conditions in combination with other agents, including an inhibitor of glycine transporter GlyT1 activity .

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of the present invention or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of the present invention is preferred. However, the combination therapy may also includes therapies in which the compound of the present invention and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of the present invention.

The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds. Likewise, compounds of the present invention may be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

Accordingly, the subject compounds may be used alone or in combination with other agents which are known to be beneficial in the subject indications or other drugs that affect receptors or enzymes that either increase the efficacy, safety, convenience, or reduce unwanted side effects or toxicity of the compounds of the present invention. The subject compound and the other agent may be co-administered, either in concomitant therapy or in a fixed combination.

In one embodiment, the subject compound may be employed in combination with anti-Alzheimer's agents, beta-secretase inhibitors, gamma-secretase inhibitors, HMG-CoA reductase inhibitors, NSAID's including ibuprofen, vitamin E, and anti-amyloid antibodies.

In another embodiment, the subject compound may be employed in combination with sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, cyclopyrrolones, imidazopyridines, pyrazolopyrimidines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, benzodiazepines, barbiturates, 5HT-2 antagonists, and the like, such as: adinazolam, allobarbitol, alonimid, alprazolam, amisulpride, amitriptyline, amobarbital, amoxapine, aripiprazole, bentazepam, benzocetamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, clomipramine, clonazepam, cloperidone, clorazepate, chlordiazepoxide, clorethate, chlorpromazine, clozapine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flupentixol, fluphenazine, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, haloperidol, hydroxyzine, imipramine, lithium, lorazepam, lormetazepam, maprotiline, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, midafur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, olanzapine, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, quetiapine, reclazepam, risperidone, roletamide, secobarbital,

sertraline, suproclone, temazepam, thioridazine, thiothixene, tracazolate, tranlycypromaine, trazodone, triazolam, trepam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, ziprasidone, zolazepam, zolpidem, and salts thereof, and combinations thereof, and the like, or the subject compound may be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

In another embodiment, the subject compound may be employed in combination with levodopa (with or without a selective extracerebral decarboxylase inhibitor such as carbidopa or benserazide), anticholinergics such as biperiden (optionally as its hydrochloride or lactate salt) and trihexyphenidyl (benzhexol) hydrochloride, COMT inhibitors such as entacapone, MOA-B inhibitors, antioxidants, A2a adenosine receptor antagonists, cholinergic agonists, NMDA receptor antagonists, serotonin receptor antagonists and dopamine receptor agonists such as alentemol, bromocriptine, fenoldopam, lisuride, naxagolide, pergolide and pramipexole. It will be appreciated that the dopamine agonist may be in the form of a pharmaceutically acceptable salt, for example, alentemol hydrobromide, bromocriptine mesylate, fenoldopam mesylate, naxagolide hydrochloride and pergolide mesylate. Lisuride and pramipexol are commonly used in a non-salt form.

In another embodiment, the subject compound may be employed in combination with a compound from the phenothiazine, thioxanthene, heterocyclic dibenzazepine, butyrophenone, diphenylbutylpiperidine and indolone classes of neuroleptic agent. Suitable examples of phenothiazines include chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine and trifluoperazine. Suitable examples of thioxanthenes include chlorprothixene and thiothixene. An example of a dibenzazepine is clozapine. An example of a butyrophenone is haloperidol. An example of a diphenylbutylpiperidine is pimozide. An example of an indolone is molindolone. Other neuroleptic agents include loxapine, sulpiride and risperidone. It will be appreciated that the neuroleptic agents when used in combination with the subject compound may be in the form of a pharmaceutically acceptable salt, for example, chlorpromazine hydrochloride, mesoridazine besylate, thioridazine hydrochloride, acetophenazine maleate, fluphenazine hydrochloride, flurphenazine enathate, fluphenazine decanoate, trifluoperazine hydrochloride, thiothixene hydrochloride, haloperidol decanoate, loxapine succinate and molindone hydrochloride. Perphenazine, chlorprothixene, clozapine, haloperidol, pimozide and risperidone are commonly used in a non-salt form. Thus, the subject compound may be employed in combination with acetophenazine, alentemol, aripiprazole, amisulpride, benzhexol, bromocriptine, biperiden, chlorpromazine, chlorprothixene, clozapine, diazepam, fenoldopam, fluphenazine, haloperidol, levodopa, levodopa with benserazide, levodopa with carbidopa, lisuride, loxapine, mesoridazine, molindolone, naxagolide, olanzapine, pergolide, perphenazine, pimozide,

pramipexole, quetiapine, risperidone, sulpiride, tetrabenazine, trihexyphenidyl, thioridazine, thiothixene, trifluoperazine or ziprasidone.

In another embodiment, the subject compound may be employed in combination with an anti-depressant or anti-anxiety agent, including norepinephrine reuptake inhibitors (including tertiary amine tricyclics and secondary amine tricyclics), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α -adrenoreceptor antagonists, neurokinin-1 receptor antagonists, atypical anti-depressants, benzodiazepines, 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, and corticotropin releasing factor (CRF) antagonists. Specific agents include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine; amoxapine, desipramine, maprotiline, nortriptyline and protriptyline; fluoxetine, fluvoxamine, paroxetine and sertraline; isocarboxazid, phenelzine, tranylcypromine and selegiline; moclobemide; venlafaxine; duloxetine; aprepitant; bupropion, lithium, nefazodone, trazodone and viloxazine; alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam and prazepam; buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof.

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention are effective for use in humans.

The term "composition" as used herein is intended to encompass a product comprising specified ingredients in predetermined amounts or proportions, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. This term in relation to pharmaceutical compositions is intended to encompass a product comprising one or more active ingredients, and an optional carrier comprising inert ingredients, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. In general, pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to

produce the desired effect upon the process or condition of diseases. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. Compositions for oral use may also be presented as hard gelatin capsules wherein the active ingredients are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil. Aqueous suspensions, oily suspensions, dispersible powders or granules, oil-in-water emulsions, and sterile injectable aqueous or oleagenous suspension may be prepared by standard methods known in the art.

In the treatment of conditions which require inhibition of glycine transporter GlyT1 activity an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900, and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day. This dosage regimen may be adjusted to provide the optimal therapeutic response. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

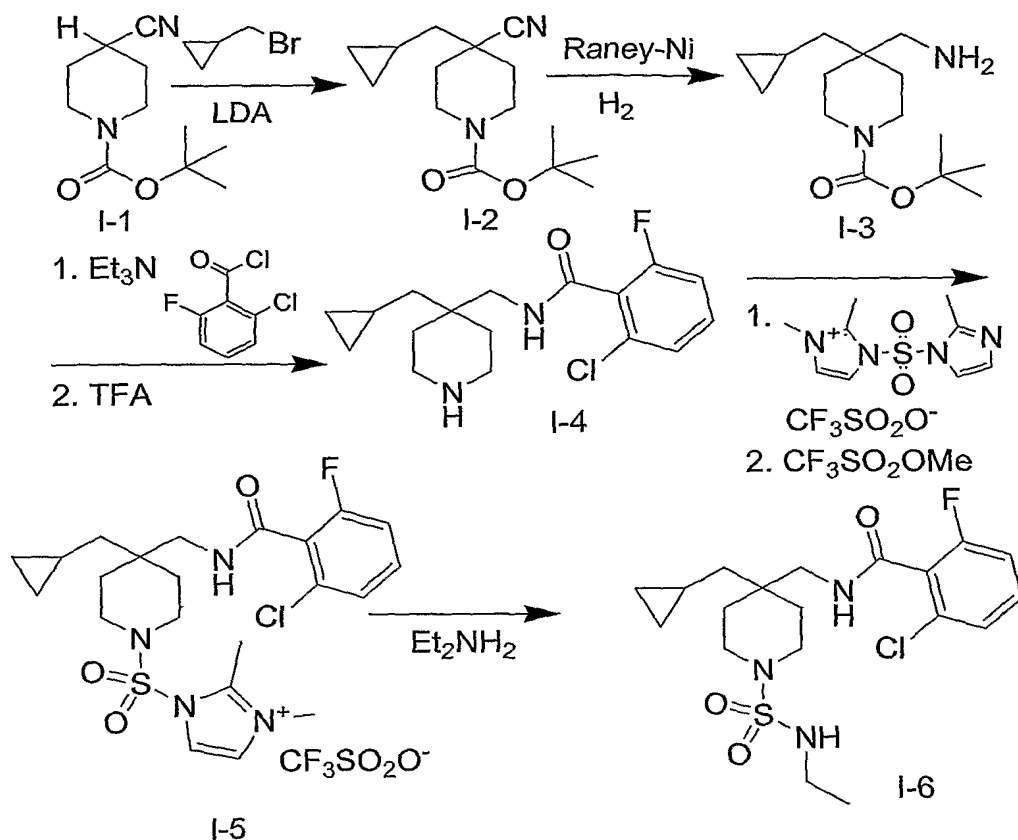
Abbreviations used in the description of the chemistry and in the Examples that follow are: CH₂Cl₂ dichloromethane; DIEA diisopropylethylamine; PS-DIEA polystyrene diisopropylethylamine; PS-DMAP polystyrene 4-*N,N*-dimethylaminopyridine; DCC dicyclohexylcarbodiimide; Ra-Ni Raney Nickel; HOBt hydroxybenzotriazole; THF tetrahydrofuran; TFA trifluoroacetic acid; MeOH methanol.

5 Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials and the requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures or as illustrated herein.

10 The compounds of this invention may be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. Substituent numbering as shown in the schemes does not necessarily correlate to that used in the claims and often, for clarity, a single substituent is shown attached to the compound where multiple substituents are allowed under the definitions hereinabove. Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the schemes and examples herein, in addition to other standard manipulations such as ester
15 hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures.

20 In some cases the final product may be further modified, for example, by manipulation of substituents. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art. In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

EXAMPLE 1



tert-Butyl 4-cyano-4-cyclopropylmethylpiperidine-1-carboxylate (I-2)

n-Butyllithium in hexanes (1.6M, 11.2 mL, 17.9 mmol) was added dropwise to diisopropylamine (2.5 mL, 17.8 mmol) in THF (20 mL) cooled in an ice bath. After stirring for 0.5 h, the solution was cooled in a dry-ice bath and a solution of *tert*-butyl 4-cyanopiperidine-1-carboxylate (I-1) (2.50 g, 11.9 mmol) in THF (20 mL) was added dropwise. The solution was stirred in a dry-ice bath for 1 h then cyclopropylmethyl bromide (1.27 mL, 13.1 mmol) was added. The reaction mixture was allowed to warm to room temperature over 2 h then quenched with water. The mixture was extracted with DCM (3X). The combined organic phase was washed with brine, dried (MgSO₄) and the solvent removed *in vacuo*. Biotage chromatography (5-10% ethyl acetate-hexanes) afforded *tert*-butyl 4-cyano-4-cyclopropylmethylpiperidine-1-carboxylate (I-2) as a colourless oil. ¹H NMR (500 MHz, CDCl₃): δ 4.12 (br s, 2H), 3.05 (br s, 2H), 2.02 (m, 2H), 1.52 (d, J = 7.0, 2H), 1.46 (s, 9H), 0.89 (m, 1H), 0.58 (m, 2H), 0.19 (m, 2H).

tert-Butyl 4-aminomethyl-4-cyclopropylmethylpiperidine-1-carboxylate (I-3)

A solution of the *tert*-butyl 4-cyano-4-cyclopropylmethylpiperidine-1-carboxylate (I-2) (1.00 g, 3.78 mmol) in ethanol (5 mL) was added to 1M sodium hydroxide in 95% ethanol-water (75 mL) and the solution degassed with nitrogen. Raney Nickel (50% slurry in water) (2.6 g) was added and the black suspension shaken under hydrogen pressure (40 psi) at room temperature for 12 h. The catalyst was filtered off and washed with 95% ethanol-water. The filtrate was evaporated *in vacuo* then partitioned between water and DCM. The organic phase was separated and the aqueous phase re-extracted with DCM twice. The combined organic phase was dried (MgSO₄) and the solvent removed *in vacuo* to leave *tert*-butyl 4-aminomethyl-4-cyclopropylmethylpiperidine-1-carboxylate (I-3) that was used in the next step without further purification. ¹H NMR (500 MHz, CDCl₃): δ 3.44 (m, 2H), 3.32 (m, 2H), 2.71 (s, 2H), 1.41 (s, 9H), 1.46-1.38 (m, 4H), 1.28 (d, J = 6.7, 2H), 1.46 (s, 9H), 0.60 (m, 1H), 0.46 (m, 2H), 0.05 (m, 2H).

2-Chloro-6-fluoro-N-{{4-cyclopropylmethylpiperidin-4-yl}methyl}benzamide (I-4)

Triethylamine (0.65 mL, 4.64 mmol) followed by 2-chloro-6-fluorobenzoyl chloride (896 mg, 4.64 mmol) were added to a solution of *tert*-Butyl 4-aminomethyl-4-cyclopropylmethylpiperidine-1-carboxylate (I-3) (1.04 g, 3.87 mmol) in DCM (5 mL) under nitrogen, cooled in an ice bath. The white suspension was allowed to warm to room temperature and then stirred for 12 h. Water was added and the organic phase separated. The aqueous phase was re-extracted with DCM. The combined organic phase was washed with saturated aqueous sodium bicarbonate solution, brine, dried (MgSO₄) and the solvent removed *in vacuo*. Biotage chromatography (20% ethyl acetate-hexanes) afforded the BOC protected product (1.52 g) that was directly deprotected. A solution of the BOC protected product in TFA (50 mL) and DCM (75 mL) was stirred at room temperature for 0.5 h then the volatile components removed *in vacuo*. The residue was partitioned between saturated sodium bicarbonate solution and DCM. The organic phase was separated and washed with saturated sodium bicarbonate solution, water, brine, dried (MgSO₄) and the solvent removed *in vacuo* to leave 2-chloro-6-fluoro-N-{{4-cyclopropylmethylpiperidin-4-yl}methyl}benzamide (I-4) as a white foam. MS 325 (M+H).

1-{{4-{{2-Chloro-6-fluorobenzoyl}amino}methyl}}-4-(cyclopropylmethyl)piperidin-1-yl}sulfonyl}-2,3-dimethyl-1H-imidazol-3-ium trifluoromethanesulfonate (I-5)

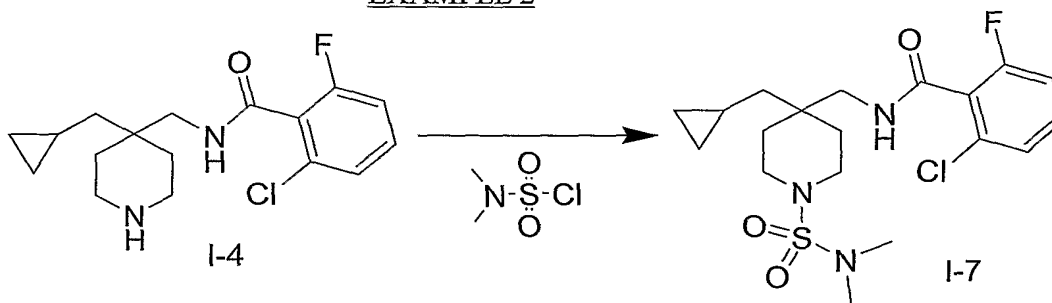
A solution of 2-chloro-6-fluoro-N-{{4-cyclopropylmethylpiperidin-4-yl}methyl}benzamide (I-4) in acetonitrile (2.5 mL) was added to a solution of 2,3-dimethyl-1-[(2-methyl-1H-imidazol-1-yl)sulfonyl]-1H-imidazol-3-ium trifluoromethanesulfonate (for synthesis see J. Org. Chem., 2003, 68, 115) (361 mg, 0.925 mmol) in acetonitrile (2 mL). The yellow solution was stirred at room temperature for 12 h then the solvent removed *in vacuo*. Biotage chromatography (2% methanol-

DCM) afforded 2-chloro-*N*-{[4-cyclopropylmethyl]-1-[(2-methyl-1*H*-imidazol-1-ylsulfonyl)]-piperidin-4-yl)methyl} 6-fluoro-benzamide (144 mg) that was directly methylated. A solution of methyl triflate (0.031 mL, 0.27 mmol) in DCM (1 mL) was added dropwise to a stirred solution of 2-chloro-*N*-{[4-cyclopropylmethyl]-1-[(2-methyl-1*H*-imidazol-1-ylsulfonyl)]-piperidin-4-yl)methyl} 6-fluoro-benzamide (118 mg) in DCM (2 mL) cooled in an ice bath. The solution was stirred in an ice bath for 1.5 h then the volatile components removed *in vacuo* to leave 1-{[4-{[2-chloro-6-fluorobenzoyl]amino]methyl}-4-(cyclopropylmethyl)piperidin-1-yl]sulfonyl}-2,3-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (I-5) that was used in the next step without further purification. MS 483 (M^+).

10 2-Chloro-*N*-{[4-cyclopropylmethyl]-1-[(ethylaminosulfonyl)]-piperidin-4-yl)methyl} 6-fluoro-benzamide (I-6)

A solution of ethylamine in THF (2.0M), 0.084 mL, 0.17 mmol) was added to a solution of 1-{[4-{[2-chloro-6-fluorobenzoyl]amino]methyl}-4-(cyclopropylmethyl)piperidin-1-yl]sulfonyl}-2,3-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (I-5) (0.084 mmol) in acetonitrile at room temperature under nitrogen. The solution was heated at 80 C for 18 h. After cooling to room temperature, the volatile components were removed *in vacuo* and the residue partitioned between water and ethyl acetate. The organic phase was separated and washed with 1N hydrochloric acid solution, 1N sodium hydroxide solution, water, brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. Preparative TLC (40% ethyl acetate-hexanes) afforded 2-Chloro-*N*-{[4-cyclopropylmethyl]-1-[(ethylaminosulfonyl)]-piperidin-4-yl)methyl} 6-fluoro-benzamide (I-6) as a glass. 1H NMR (500 MHz, CD_3OD): δ 7.42 (m, 1 H); 7.30 (d, $J = 7.8$ Hz, 1 H); 7.16 (t, $J = 8.4$ Hz, 1 H); 3.52 (s, 2 H); 3.26 (m, 4 H); 3.21 (m, 2 H); 3.03 (m, 2 H); 1.69 (s, 4 H); 1.37 (d, $J = 6.2$ Hz, 2 H); 1.16 (t, $J = 7.0$ Hz, 3 H); 0.77 (s, 1 H); 0.49 (d, $J = 6.6$ Hz, 2 H); 0.08 (s, 2 H); MS 432 ($M+H$).

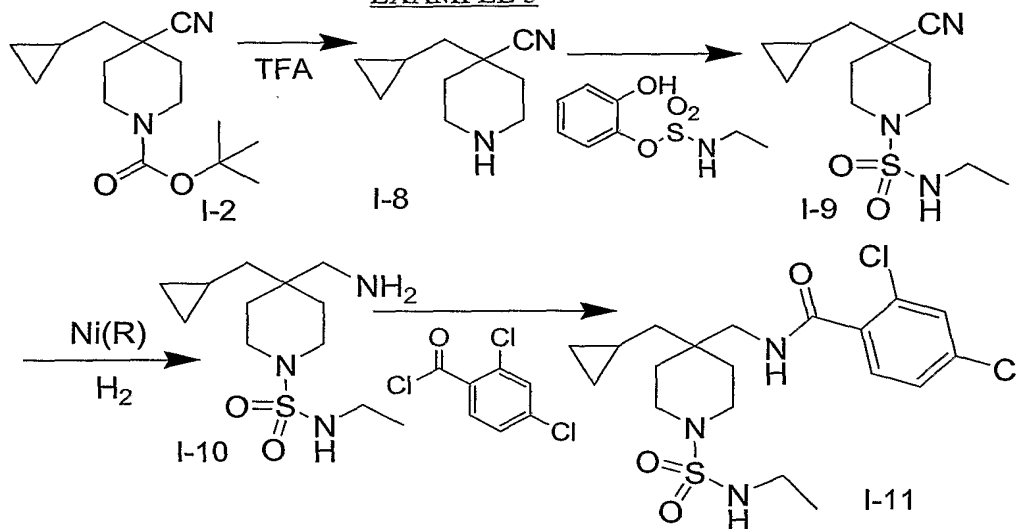
25 EXAMPLE 2



2-Chloro-*N*-{[4-cyclopropylmethyl]-1-[(dimethylaminosulfonyl)]-piperidin-4-yl)methyl} 6-fluoro-benzamide (I-7)

Triethylamine (0.026 mL, 0.19 mmol) followed by dimethylsulfamoyl chloride (0.020 mL, 0.19 mmol) were added to a solution of 2-chloro-6-fluoro-*N*-{[4-cyclopropylmethylpiperidin-4-yl]methyl}benzamide (I-4) (50 mg, 0.154 mmol) in DCM (2 mL) at room temperature. The solution was stirred at room temperature for 48 h then the volatile components removed *in vacuo*. Preparative TLC afforded 2-Chloro-*N*-{[4-cyclopropylmethyl)-1-[(dimethylaminosulfonyl)]-piperidin-4-yl]methyl}6-fluoro-benzamide (I-7). ¹H NMR (500 MHz, CDCl₃): δ 7.35-7.29 (m, 1 H), 7.22 (m, 1 H), 7.06 (t, *J* = 8.3 Hz, 1 H), 5.88 (s, 1 H), 3.62 (d, *J* = 6.5 Hz, 2 H), 3.38-3.30 (m, 4 H), 2.82 (s, 6 H), 1.67 (m, 4 H), 1.33 (d, *J* = 6.6 Hz, 2 H), 0.67 (m, 1 H), 0.52 (q, *J* = 5.9 Hz, 2 H), 0.06 (q, *J* = 4.9 Hz, 2 H).

EXAMPLE 3



4-Cyano-4-cyclopropylmethylpiperidine (I-8)

A solution of tert-butyl 4-cyano-4-cyclopropylmethylpiperidine-1-carboxylate (I-2) (1.00 g, 3.78 mmol) in TFA (50 mL) and DCM (75 mL) was stirred at room temperature for 0.5 h then the volatile components removed *in vacuo*. The residue was partitioned between saturated sodium bicarbonate solution and DCM. The organic phase was separated and the aqueous phase re-extracted with DCM twice. The combined organic phase was washed with brine, dried (MgSO₄) and the solvent removed *in vacuo* to leave 4-cyano-4-cyclopropylmethylpiperidine (I-8) as a glass. ¹H NMR (500 MHz, CD₃OD): δ 3.03 (d, *J* = 13.1 Hz, 2 H), 2.88-2.82 (m, 2 H), 2.00 (d, *J* = 11.7 Hz, 2 H), 1.55-1.49 (m, 4 H), 0.92-0.84 (m, 1 H), 0.57-0.55 (m, 2 H), 0.20 (q, *J* = 5.0 Hz, 2 H).

N-Ethyl-2-hydroxyl-benzenesulfonamide

A solution of catechol sulfate (911 mg, 5.29 mmol) in DCM (2 mL) was added to a solution of triethylamine (0.65 g, 0.89 mL, 6.35 mmol) and ethylamine (2M solution in THF, 3.17 mL,

6.35 mmol) at 0 °C with vigorous stirring. The mixture was stirred for 2.5 hours at 0 °C then poured into 0.3 M HCl solution (100 ml) and extracted with diethyl ether (3 x 25 ml). The combined organic extracts were washed with water (6 x 50 ml), dried over MgSO₄, filtered, and evaporated to give a yellow oil. The crude product was chromatographed on silica eluted with 5% methanol in DCM to give the title product as an orange oil. ¹H NMR δ (ppm)(CDCl₃): 7.23-7.17 (2 H, m), 7.08-7.04 (1 H, m), 6.96-6.90 (1 H, m), 6.28 (1 H, bs), 4.84 (1 H, bs), 3.33 (2 H, q, J = 7.2 Hz), 1.24 (3 H, t, J = 7.3 Hz).

4-Cyano-4-(cyclopropylmethyl)-N-ethylpiperidine-1-sulfonamide (I-9)

A solution of 4-cyano-4-cyclopropylmethylpiperidine (I-8) (400 mg, 2.43 mmol) and N-ethyl-2-hydroxyl-benzenesulfonamide (529 mg, 2.43 mmol) in dioxane (15 mL) was heated at reflux for 5 h. After cooling to room temperature, the reaction mixture was poured onto 1N hydrochloric acid solution and extracted with diethyl ether twice. The combined organic phase was washed with water, brine, dried (MgSO₄) and the solvent removed *in vacuo*. Biotage chromatography (0.5 – 1% methanol-DCM) afforded a colourless oil (448 mg). The oil was dissolved in DCM and washed with 2N sodium hydroxide solution twice, water, brine, dried (MgSO₄) and the solvent removed *in vacuo* to leave 4-cyano-4-(cyclopropylmethyl)-N-ethylpiperidine-1-sulfonamide (I-9) as a colourless oil. ¹H NMR (500 MHz, CD₃OD): δ 3.68 (d, J = 12.8 Hz, 2 H), 3.06-2.96 (m, 4 H), 2.10 (d, J = 11.6 Hz, 2 H), 1.69-1.63 (m, 2 H), 1.57 (d, J = 6.9 Hz, 2 H), 1.16 (t, J = 7.2 Hz, 3 H), 0.93-0.85 (m, 1 H), 0.59-0.55 (m, 2 H), 0.21 (q, J = 5.0 Hz, 2 H).

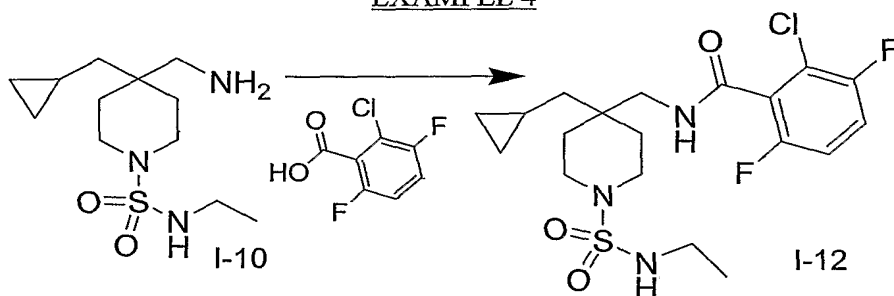
4-Aminomethyl-4-(cyclopropylmethyl)-N-ethylpiperidine-1-sulfonamide (I-10)

A solution of 4-cyano-4-(cyclopropylmethyl)-N-ethylpiperidine-1-sulfonamide (I-9) (83 mg, 0.306 mmol) in ethanol (1 mL) was added to 1M sodium hydroxide in 95% ethanol-water (15 mL) and the solution degassed with nitrogen. Raney Nickel (50% slurry in water) (220 mg) was added and the black suspension shaken under hydrogen pressure (40 psi) at room temperature for 12 h. The catalyst was filtered off and washed with 95% ethanol-water. The filtrate was evaporated *in vacuo* then partitioned between water and DCM. The organic phase was separated and the aqueous phase re-extracted with DCM twice. The combined organic phase was dried (MgSO₄) and the solvent removed *in vacuo* to leave 4-aminomethyl-4-(cyclopropylmethyl)-N-ethylpiperidine-1-sulfonamide (I-10) that was used in the next step without further purification. ¹H NMR (500 MHz, CD₃OD): δ 3.21-3.11 (m, 4 H), 3.02 (q, J = 7.2 Hz, 2 H), 2.69 (s, 2 H), 1.63-1.53 (m, 4 H), 1.31 (m, 2 H), 1.15 (t, J = 7.2 Hz, 3 H), 0.65 (m, 1 H), 0.48 (t, J = 6.4 Hz, 2 H), 0.07 (m, 2 H).

2,4-Dichloro-N-[[4-cyclopropylmethyl]-1-[(ethylaminosulfonyl)]-piperidin-4-yl]methyl}benzamide (I-11)

Triethylamine (0.027 mL, 0.19 mmol) followed by 2,4-dichlorobenzoyl chloride (0.027 mL, 0.19 mmol) were added to a solution of leave 4-aminomethyl-4-(cyclopropylmethyl)-N-ethylpiperidine-1-sulfonamide (I-10) (35 mg, 0.127 mmol) in DCM (1 mL) under nitrogen, cooled in an ice bath. The reaction mixture was allowed to warm to room temperature and then stirred for 12 h. Water was added and the organic phase separated. The aqueous phase was re-extracted with DCM. The combined organic phase was washed with saturated aqueous sodium bicarbonate solution, brine, dried (MgSO₄) and the solvent removed *in vacuo*. Preparative TLC (40% ethyl acetate-hexanes) afforded 2,4-dichloro-N-[[4-cyclopropylmethyl]-1-[(ethylaminosulfonyl)]-piperidin-4-yl]methyl}benzamide (I-11) as a glass. ¹H NMR (500 MHz, CD₃OD): δ 7.54 (d, *J* = 1.4 Hz, 1 H), 7.43-7.39 (m, 2 H), 3.49 (s, 2 H), 3.26 (m, 2 H), 3.21-3.15 (m, 2 H), 3.03 (q, *J* = 7.2 Hz, 2 H), 1.68 (t, *J* = 5.7 Hz, 4 H), 1.38 (d, *J* = 6.7 Hz, 2 H), 1.15 (t, *J* = 7.2 Hz, 3 H), 0.81-0.73 (m, 1 H), 0.50-0.48 (m, 2 H), 0.08 (q, *J* = 4.9 Hz, 2 H); MS 448 (M+H).

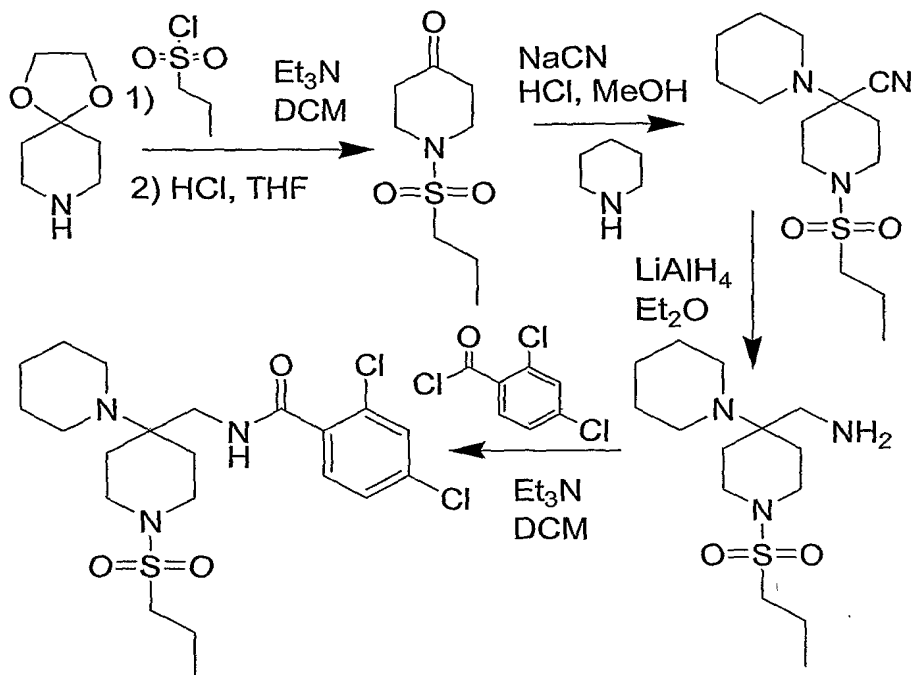
EXAMPLE 4



2-Chloro-N-[[4-cyclopropylmethyl]-1-[(ethylaminosulfonyl)]-piperidin-4-yl]methyl}-3,6-difluorobenzamide (I-12)

4-Aminomethyl-4-(cyclopropylmethyl)-N-ethylpiperidine-1-sulfonamide (I-10) was treated with 2-chloro-3,6-difluorobenzoyl chloride according to the procedure outlined above to afford 2-chloro-N-[[4-cyclopropylmethyl]-1-[(ethylaminosulfonyl)]-piperidin-4-yl]methyl}-3,6-difluorobenzamide (I-12). ¹H NMR (500 MHz, CD₃OD): δ 7.37-7.31 (m, 1 H), 7.24-7.18 (m, 1 H), 3.53 (s, 2 H), 3.26-3.18 (m, 4 H), 3.04 (q, *J* = 7.2 Hz, 2 H), 1.69 (t, *J* = 5.7 Hz, 4 H), 1.37 (d, *J* = 6.7 Hz, 2 H), 1.16 (t, *J* = 7.2 Hz, 3 H), 0.81-0.73 (m, 1 H), 0.50 (q, *J* = 5.9 Hz, 2 H), 0.08 (q, *J* = 4.8 Hz, 2 H); MS 450 (M+H).

EXAMPLE 5



1-(propylsulfonyl)piperidin-4-one

Propane sulfonyl chloride (16.5 mL, 147 mmol) was added dropwise over 20 min to a cooled (0°C) solution of 4-piperidine ethylene ketal (20.0 g, 140 mmol) and triethylamine (23.4 mL, 168 mmol) in dichloromethane (300 mL). On complete addition the mixture was allowed to warm to ambient temperature and stirred for 2h. The mixture was evaporated and the residue dissolved in tetrahydrofuran (200 mL) and 5N hydrochloric acid (150 mL) and the resulting solution stirred for 18 h. The tetrahydrofuran was removed under reduced pressure and the aqueous phase was extracted with diethyl ether (2X200 mL). Some of the desired product remained in the aqueous phase so the pH was adjusted to 7 by the addition of 4 N sodium hydroxide and the aqueous phase extracted with diethyl ether (2X200 mL), ethyl acetate (200 mL) and dichloromethane (200 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated to give 1-(propylsulfonyl)piperidin-4-one as an off white solid which was used in the next step without further purification. ^1H NMR (360 MHz, CDCl_3): δ 3.56 (t, $J = 6.1$ Hz, 4 H); 2.94-2.90 (m, 2 H); 2.50 (t, $J = 6.1$ Hz, 4 H); 1.85-1.70 (m, 2 H); 1.04-0.96 (m, 3 H).

1'-(propylsulfonyl)-1,4'-bipiperidine-4'-carbonitrile

Sodium cyanide (0.98 g, 20.0 mmol) was added to a solution of piperidine (1.98 mL, 20.0 mmol) in 1 N hydrochloric acid (20 mL). A solution of 1-(propylsulfonyl)piperidin-4-one (4.11 g, 20.0 mmol) in methanol (40 mL) was added dropwise to the mixture over 30min. On complete addition the

5 mixture was allowed to warm to ambient temperature and stirred for 18 h. The precipitate was filtered and washed with water (10 mL) and dried under high vacuum at 60 °C which gave a white solid. The volume of the filtrate was reduced to approx 20 mL and the pH of the aqueous residue was adjusted to 7 by the addition of 4 N sodium hydroxide solution. The aqueous phase was extracted with ethyl acetate (2X100 mL) and dichloromethane (2X100 mL). The combined organics were dried over anhydrous sodium sulfate, filtered and evaporated to give 1'-(propylsulfonyl)-1,4'-bipiperidine-4'-carbonitrile as a colourless oil. ¹H NMR (400 MHz, CDCl₃): δ 3.70-3.64 (m, 2 H); 3.09-3.03 (m, 2 H); 2.85-2.81 (m, 2 H); 2.51 (t, J = 5.0 Hz, 4 H); 2.15 (d, J = 13.6 Hz, 2 H); 1.83-1.75 (m, 4 H); 1.58-1.54 (m, 4 H); 1.45-1.39 (m, 2 H); 1.00 (t, J = 7.5 Hz, 3 H).

10 {[1'-(propylsulfonyl)-1,4'-bipiperidin-4'-yl]methyl}amine

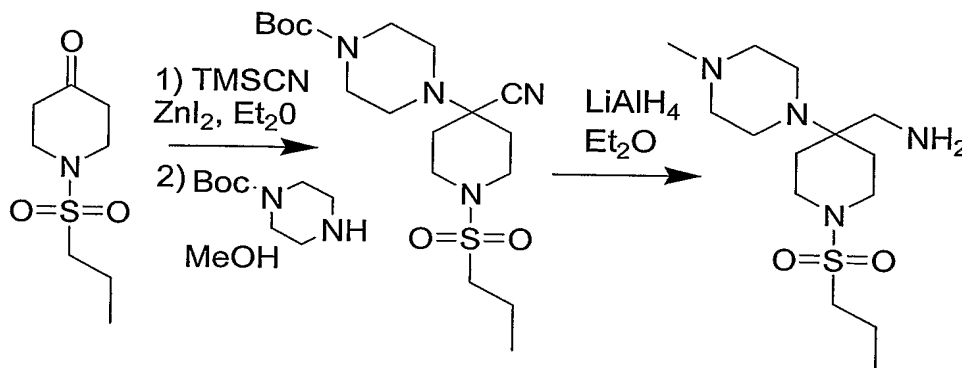
To a solution of lithium aluminium hydride in diethyl ether (1 M, 1.6 mL) at -78 °C was added a solution of 1'-(propylsulfonyl)-1,4'-bipiperidine-4'-carbonitrile (0.40 g, 1.34 mmol) in diethyl ether (10 mL) over 30 min. The mixture was stirred cold for 1 h then allowed to warm to room temperature and stirred for 2 h. The resultant mixture was cooled in an ice-bath and to the mixture was added water (0.17 mL), 15% NaOH solution (0.17 mL) then water (0.17 mL). The resultant white granular solid was filtered off and the filter-cake rinsed twice with diethyl ether. The filtrate was evaporated to give {[1'-(propylsulfonyl)-1,4'-bipiperidin-4'-yl]methyl}amine as a clear oil which was used in the next step without further purification; *m/z* (ES⁺) 304 (M⁺+H).

20 2,4-dichloro-*N*-{[1'-(propylsulfonyl)-1,4'-bipiperidin-4'-yl]methyl}benzamide

{[1'-(propylsulfonyl)-1,4'-bipiperidin-4'-yl]methyl} (0.40 g, 1.32 mmol) in dichloromethane (6 mL) and triethylamine (0.37 mL, 2.64 mmol) was treated with 2,4-dichlorobenzoyl chloride at 0 °C. The reaction was stirred at 0 °C for 30 min, then allowed to warm to room temperature for 30 min. The resulting mixture was partitioned between dichloromethane and water. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate and evaporated to dryness. Purification by flash column chromatography on silica gel, eluting with dichloromethane (containing 1% 0.880 ammonia) on a gradient of methanol gave 2,4-dichloro-*N*-{[1'-(propylsulfonyl)-1,4'-bipiperidin-4'-yl]methyl}benzamide (190 mg) as a white foam. This foam was triturated with diethyl ether/*iso*-hexane (1:1) and the resulting solid dissolved in hot ethanol (minimum amount). Oxalic acid (2 eq in minimum amount ethanol) was added and the mixture allowed to cool. 2,4-dichloro-*N*-{[1'-(propylsulfonyl)-1,4'-bipiperidin-4'-yl]methyl}benzamide (oxalate salt) crystallized and was filtered to give a white solid. ¹H NMR (free base) (400 MHz, CDCl₃): δ 7.72 (d, J = 8.4 Hz, 1 H); 7.44 (d, J = 2.0 Hz, 1 H); 7.37-7.33

(m, 1 H); 7.03 (s, 1 H); 3.59 (dd, $J = 0.0, 5.2$ Hz, 4 H); 3.15-3.09 (m, 2 H); 2.91-2.87 (m, 2 H); 2.58 (s, 4 H); 2.00-1.94 (m, 2 H); 1.90-1.80 (m, 2 H); 1.60-1.40 (m, 8 H); 1.07 (t, $J = 7.4$ Hz, 3 H).

EXAMPLE 6



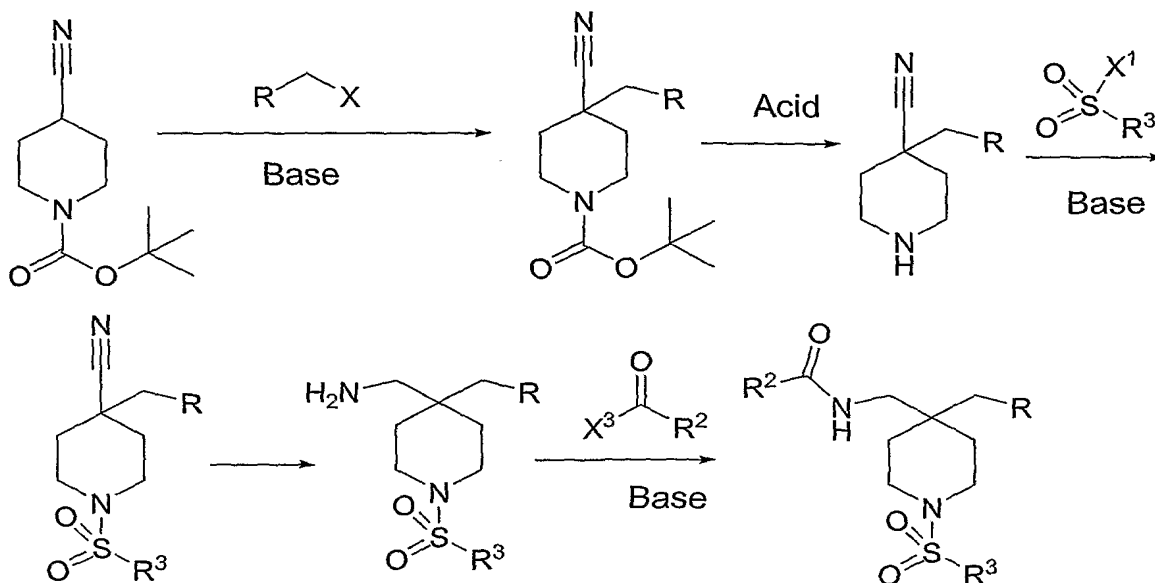
tert-Butyl 4-[4-cyano-1-(propylsulfonyl)piperidin-4-yl]piperazine-1-carboxylate

To a flask in an ice-bath was added 1-(propylsulfonyl)piperidin-4-one (5.0 g, 24.4 mmol), trimethylsilylcyanide (3.25 mL, 24.2 mmol) and diethyl ether (3 mL) followed by addition of zinc iodide (0.005 g). This gave a yellow suspension which turned to an orange solution after 20 min stirring at room temperature. To the solution was added a solution of *tert*-butyl piperazine-1-carboxylate (4.54 g, 24.4 mmol) in methanol (35 mL). The solution was then refluxed overnight. The reaction was cooled and more trimethylsilylcyanide (0.5 eq) and zinc iodide (0.005 g) were added. The reaction was heated at reflux overnight and no starting material remained by TLC. The reaction mixture was evaporated to dryness and the product crystallised from ethyl acetate/*iso*-hexane to give *tert*-butyl 4-[4-cyano-1-(propylsulfonyl)piperidin-4-yl]piperazine-1-carboxylate as an off-white crystalline solid. ¹H NMR (360 MHz, CDCl₃): δ 3.80 (d, $J = 13.5$ Hz, 2 H); 3.48 (t, $J = 4.9$ Hz, 4 H); 3.15-3.09 (m, 2 H); 2.93-2.89 (m, 2 H); 2.60 (t, $J = 4.9$ Hz, 4 H); 2.22 (d, $J = 13.4$ Hz, 2 H); 1.91-1.81 (m, 4 H); 1.47 (s, 9 H); 1.07 (t, $J = 7.4$ Hz, 3 H).

{[4-(4-methylpiperazin-1-yl)-1-(propylsulfonyl)piperidin-4-yl]methyl}amine

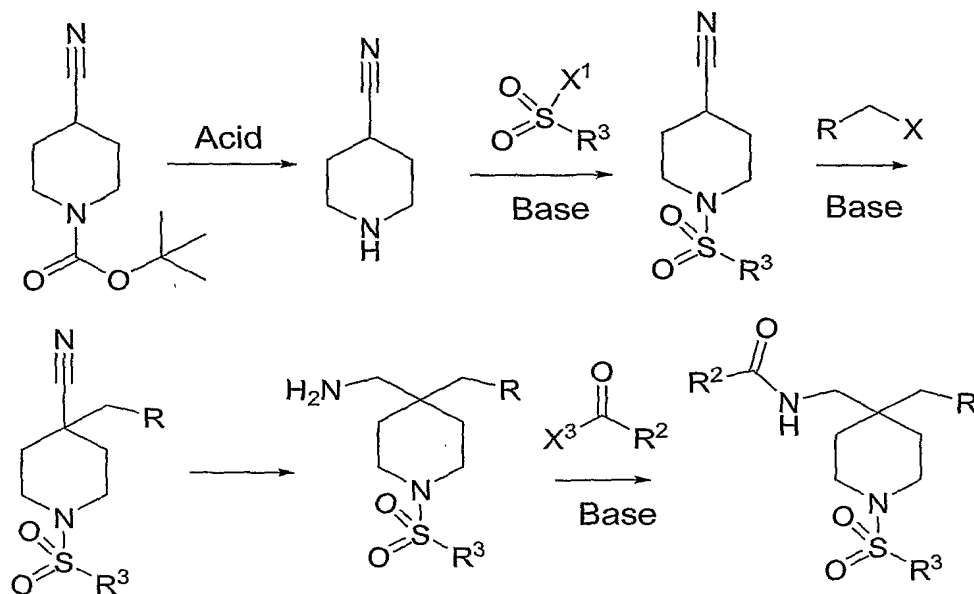
tert-Butyl 4-[4-cyano-1-(propylsulfonyl)piperidin-4-yl]piperazine-1-carboxylate was reacted with lithium aluminium hydride as in Scheme 5 to give {[4-(4-methylpiperazin-1-yl)-1-(propylsulfonyl)piperidin-4-yl]methyl}amine as a clear oil. m/z ($M^+ + H$) 319.

GENERAL SCHEME 7



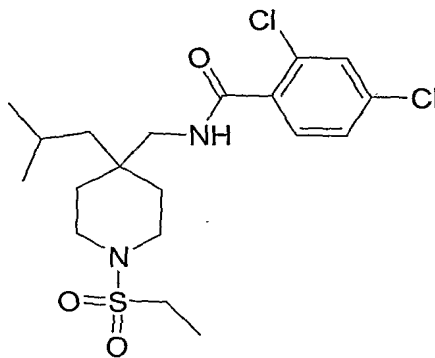
The commercially available starting material tert-butyl 4-cyanopiperidine-1-carboxylate was alkylated with an alkyl halide and base to give 4,4,-disubstituted piperidine. The protecting group was removed by methods known in the art. In the presence of base, a sulfonyl halide was then added to give a sulfonamide. The nitrile was reduced through various means including hydrogenation or hydride equivalents. The primary amine was then coupled with an acid or an acid halide in the presence of base to give the final product.

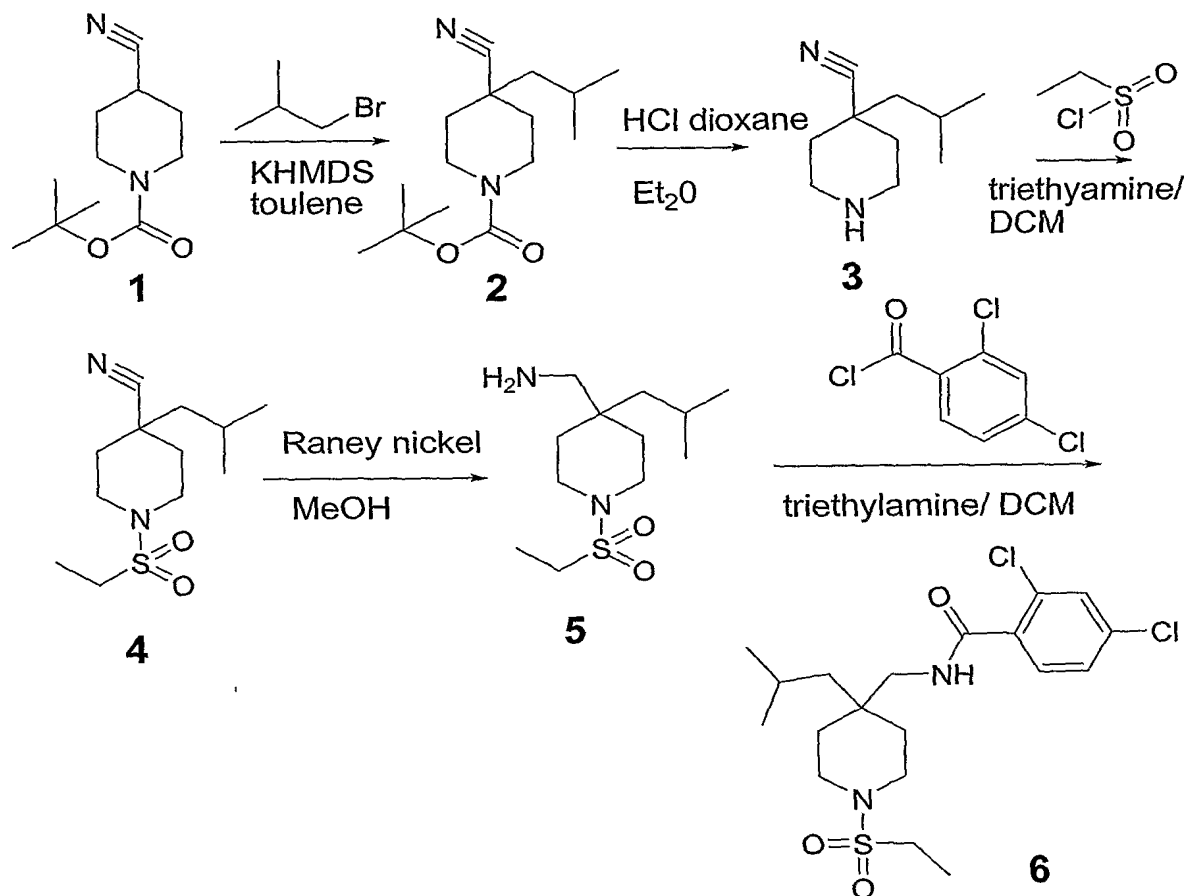
GENERAL SCHEME 8



The commercially available starting material tert-butyl 4-cyanopiperidine-1-carboxylate was deprotected in the usual manner. To this was added a sulfonylhalide in the presence of base to form the sulfonamide. The sulfonamide was deprotonated and alkylated to give the 4,4,-disubstituted piperidine. The nitrile was reduced through various means including hydrogenation or hydride equivalents. The primary amine was then coupled with an acid or an acid halide in the presence of base to give the final product.

EXAMPLE 9





tert-butyl 4-cyano-4-isobutylpiperidine-1-carboxylate(2)

In a dry round bottom flask was placed tert-butyl 4-cyanopiperidine-1-carboxylate (1) (20g, 95 mmol) and anhydrous toluene (200 ml). To this was added 1-bromo-2-methylpropane (12.41 ml, 114 mmol). Immediately after addition of 1-bromo-2-methylpropane, solid KHMDS (28.5g, 143 mmol) was added at room temperature and an exotherm was observed. The solution was allowed to stir for 12 hours monitoring by TLC (30% EtOAc/hexanes) at which time it was quenched with saturated aq. NH₄Cl solution (100 mL). To the mixture was added EtOAc (50 ml) and the solution was then extracted by dilution with 250 ml, water and 3 washes with EtOAc (75 ml each). The organic layer was washed with brine (200 ml) and dried over MgSO₄. The organic solvent was removed in vacuo to give tert-butyl 4-cyano-4-isobutylpiperidine-1-carboxylate (2) as a yellow solid. MS 267 (M+1)

4-cyano-4-isobutylpiperidinium chloride (3)

In a round bottom flask was placed *tert*-butyl 4-cyano-4-isobutylpiperidine-1-carboxylate (2, 17g, 63.8 mmol) and diethyl ether (200 mL). To the flask was added HCl in dioxane (4M, 2.327g, 63.8 mmol) and the solution stirred overnight. A fine white solid formed in suspension and was filtered with a medium frit to give 4-cyano-4-isobutylpiperidinium chloride (3) as an HCl salt in quantitative yield after washing with diethyl ether (3X 50 ml). MS 167 (M+1)

1-(ethylsulfonyl)-4-isobutylpiperidine-4-carbonitrile(4)

In a dry round bottom flask was placed 4-cyano-4-isobutylpiperidinium chloride (3, 4.49g, 44.4 mmol) dichloromethane (150ml) and triethylamine (6.1 ml, 44.4 mmol). To this was added dropwise ethanesulfonyl chloride (2.1 ml, 22.2 mmol). This was stirred 1 hour and quenched with water (100 ml). The mixture was extracted with dichloromethane (3x 50 ml) and the combined organic fractions dried (MgSO₄), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/Hexanes to give 1-(ethylsulfonyl)-4-isobutylpiperidine-4-carbonitrile (4) as a white solid. MS 259 (M+1)

1-[1-(ethylsulfonyl)-4-isobutylpiperidin-4-yl]methanamine(5)

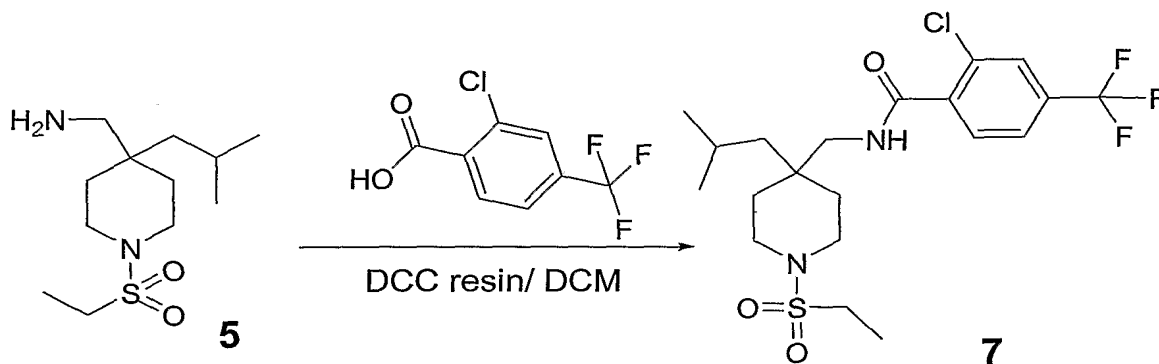
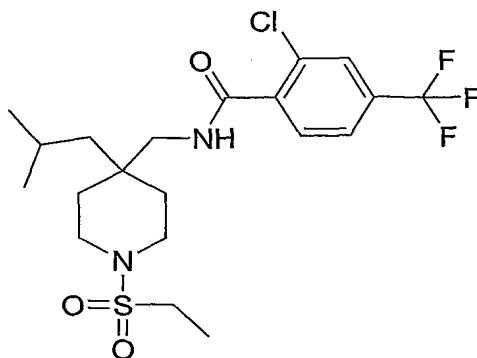
In a heavy wall flask was placed 1-(ethylsulfonyl)-4-isobutylpiperidine-4-carbonitrile (4, 1.4g, 5.42 mmol) 2N ammonia in methanol (50 ml). To this was added commercially available Raney nickel slurry in water (1.393g, 16.26 mmol). This was then agitated under hydrogen atmosphere (45 psi) at room temp for 12 hours. The catalyst was filtered off using celite and washed with MeOH (200 ml). The organics were concentrated in vacuo to give 1-[1-(ethylsulfonyl)-4-isobutylpiperidin-4-yl]methanamine (5) as a clear oil. MS 263 (M+1)

2,4-dichloro-N-[[1-(ethylsulfonyl)-4-isobutylpiperidin-4-yl]methyl]benzamide(6)

In a dry round bottom flask was placed 1-[1-(ethylsulfonyl)-4-isobutylpiperidin-4-yl]methanamine (5, 1g, 3.81 mmol), dichloromethane (150ml), and triethylamine (1.59ml, 11.43 mmol). To this was added dropwise 2,4-dichlorobenzoyl chloride (0.760ml, 4.57) and the reaction stirred 1 hour and quenched with water (100 ml). The mixture was extracted with dichloromethane (3x 50 ml) and the combined organic fractions were dried (MgSO₄), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/Hexanes to 2,4-dichloro-N-[[1-(ethylsulfonyl)-4-isobutylpiperidin-4-yl]methyl]benzamide (6) as a white solid. Calc HRMS 435.1271 Found 435.1267. ¹H NMR (300 MHz D₆DMSO): δ 8.39 (t, J = 5.4 Hz, 1 H), 7.69 (d, J = 1.8 Hz, 1 H), 7.49 (dd, J = 8.4 Hz, 1 H), 7.42 (dd, J = 8.4 Hz, 1 H), 3.31 (t, J = 5.1 Hz, 2 H), 3.21 (m, 4

H), 3.05 (q, $J = 7.2$ Hz, 2 H), 1.76 (m, 1 H), 1.5 (m, 4 H), 1.128 (d, $J = 5.1$ Hz, 2 H), 1.21 (t, $J = 7.5$ Hz, 3 H), 0.93 (s, 3 H), 0.91 (s, 3 H).

EXAMPLE 10

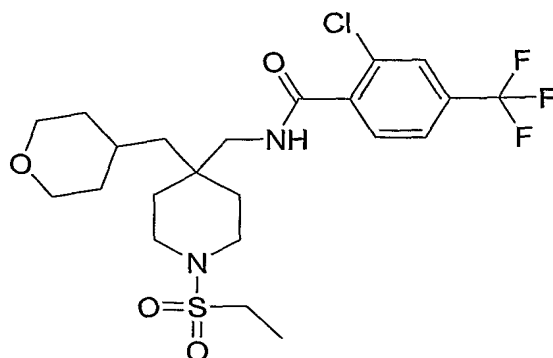


2-chloro-N-{[1-(ethylsulfonyl)-4-isobutylpiperidin-4-yl]methyl}-4-(trifluoromethyl)benzamide(7)

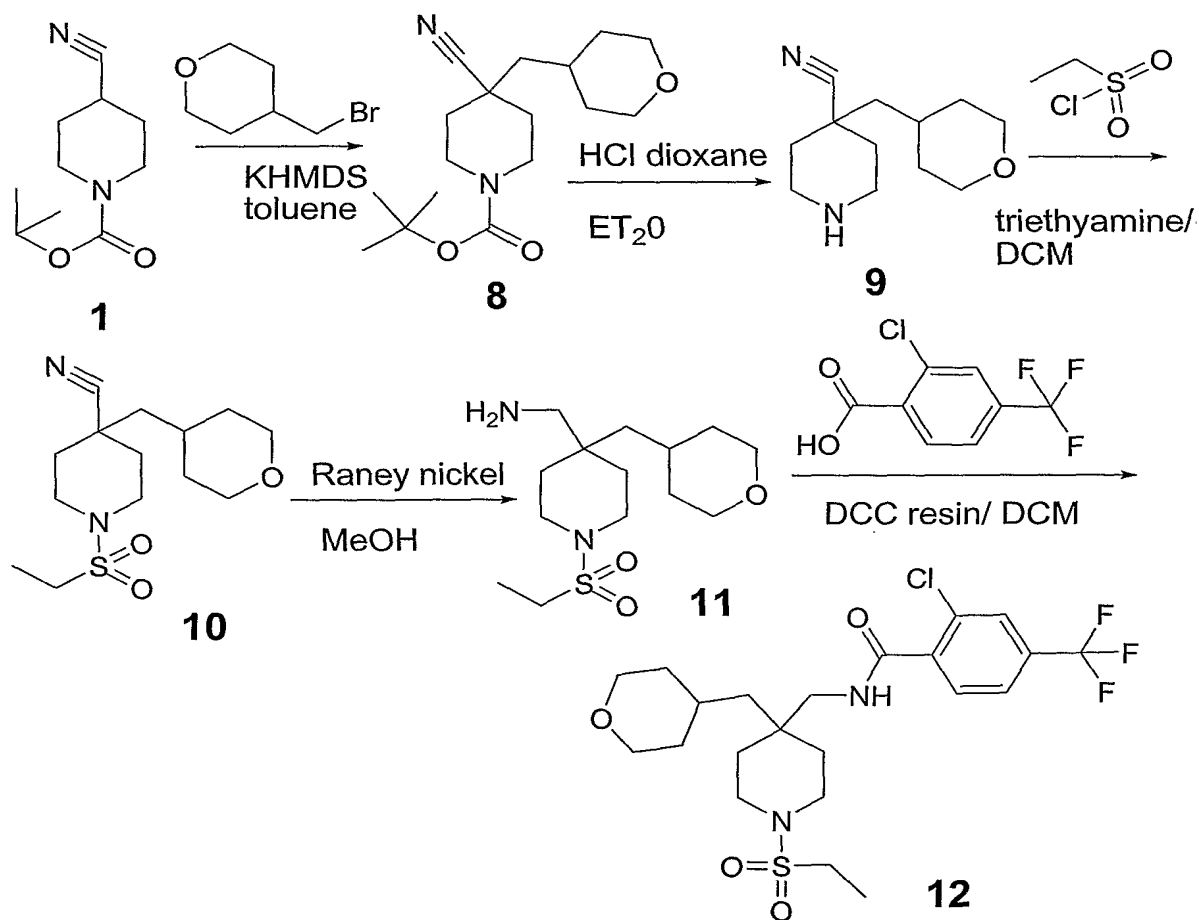
In a large glass container with a Teflon cap was placed 1-[1-(ethylsulfonyl)-4-isobutylpiperidin-4-yl]methanamine (5) (670mg, 2.55 mmol). This was dissolved in dichloromethane (50 ml) and PS-carbodiimide resin (5.11 mmol) was then added along with 2-chloro-4-(trifluoromethyl)benzoic acid (688mg, 3.06 mmol). The lid was sealed and the bottle was shaken for .5 hours. The resin was filtered off and washed with EtOAc (3X 25 ml). The organics were concentrated in vacuo to give an off white solid. The residue was purified by column chromatography on silica gel, eluting with EtOAc/Hexanes to give 2-chloro-N-{[1-(ethylsulfonyl)-4-isobutylpiperidin-4-yl]methyl}-4-(trifluoromethyl)benzamide (7) as a white solid. Calculated HRMS 469.1534 Found 469.15333. ¹H NMR (300 MHz D₆DMSO): δ 8.85 (s, 1 H), 7.95 (s, 1 H), 7.79 (d, $J = 7.8$ Hz, 1 H), 7.60 (d, $J = 8.1$ Hz, 1

H), 3.34 (s, 2 H), 3.21 (s, 4 H), 3.05 (q, $J=7.2$ Hz, 2 H), 1.75 (m, 1 H), 1.51 (m, 4 H), 1.29 (d, $J=4.8$ Hz, 2 H), 1.21 (t, $J=7.5$ Hz, 3 H), 0.94 (s, 3 H), 0.91 (s, 3H).

EXAMPLE 11



5



tert-butyl 4-cyano-4-(tetrahydro-2H-pyran-4-ylmethyl)piperidine-1-carboxylate(8)

In a dry round bottom flask was placed tert-butyl 4-cyanopiperidine-1-carboxylate (1) (20g, 95 mmol) and anhydrous toluene (200 ml). To this was added 4-(bromomethyl)tetrahydro-2H-pyran (20.44g, 114 mmol). Solid KHMDS (28.5g 143 mmol) was added in one portion and an exotherm was observed. The solution was allowed to stir for 12 hours at room temperature and monitored by TLC (30% EtOAc/hexanes) and quenched with saturated aq. NH₄Cl solution (100 ml). To the mixture was added EtOAc (50 ml) and the solution was then extracted by dilution with 250 ml. water and 3 washes with EtOAc (75 ml each). The organic layer was washed with brine (200 ml) and dried over MgSO₄. The organic solvent was removed in vacuo to give tert-butyl 4-cyano-4-(tetrahydro-2H-pyran-4-ylmethyl)piperidine-1-carboxylate (8) as a yellow solid. MS 309 (M+1)

4-cyano-4-(tetrahydro-2H-pyran-4-ylmethyl)piperidinium chloride(9)

In a round bottom flask was placed tert-butyl 4-cyano-4-(tetrahydro-2H-pyran-4-ylmethyl)piperidine-1-carboxylate (8) (5g, 16.21 mmol), diethyl ether (200 ml), and methanol (1 ml). To this was added commercially available HCl in dioxane (4M, 0.985 ml, 32.4 mmol.). The solution was stirred overnight. A fine white solid was formed in suspension and filtered with a medium frit to give 4-cyano-4-(tetrahydro-2H-pyran-4-ylmethyl)piperidinium chloride (9) as an HCl salt in quantitative yield after washing with diethyl ether (3X 50 ml). MS 209 (M+1)

1-(ethylsulfonyl)-4-(tetrahydro-2H-pyran-4-ylmethyl)piperidine-4-carbonitrile(10)

In a dry round bottom flask was placed 4-cyano-4-(tetrahydro-2H-pyran-4-ylmethyl)piperidinium chloride (9, 1g, 3.1 mmol), dichloromethane (50 ml) and triethylamine (2.162ml, 15.51 mmol). To this was added dropwise ethanesulfonyl chloride (0.317ml, 3.1 mmol). The reaction was stirred 1 hour and quenched with water (100 ml). The mixture was extracted with dichloromethane (3x 50 ml) and the combined organic fractions were dried (MgSO₄), filtered, and the solvent evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/Hexanes to give 1-(ethylsulfonyl)-4-(tetrahydro-2H-pyran-4-ylmethyl)piperidine-4-carbonitrile (10) as a white solid. MS 301 (M+1)

1-[1-(ethylsulfonyl)-4-(tetrahydro-2H-pyran-4-ylmethyl)piperidin-4-yl]methanamine(11)

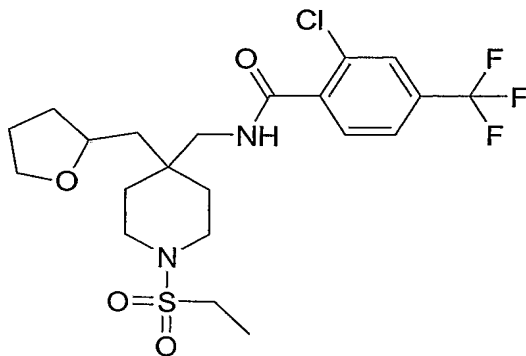
In a heavy wall flask was placed 1-(ethylsulfonyl)-4-(tetrahydro-2H-pyran-4-ylmethyl)piperidine-4-carbonitrile (10) (1.25g, 4.17 mmol) and 2N ammonia in methanol (50 ml). To this was added Raney nickel slurry in water (1.073g, 12.52 mmol) and the reaction agitated under hydrogen atmosphere (45 psi) at room temp for 12 hours. The catalyst was filtered off using celite and

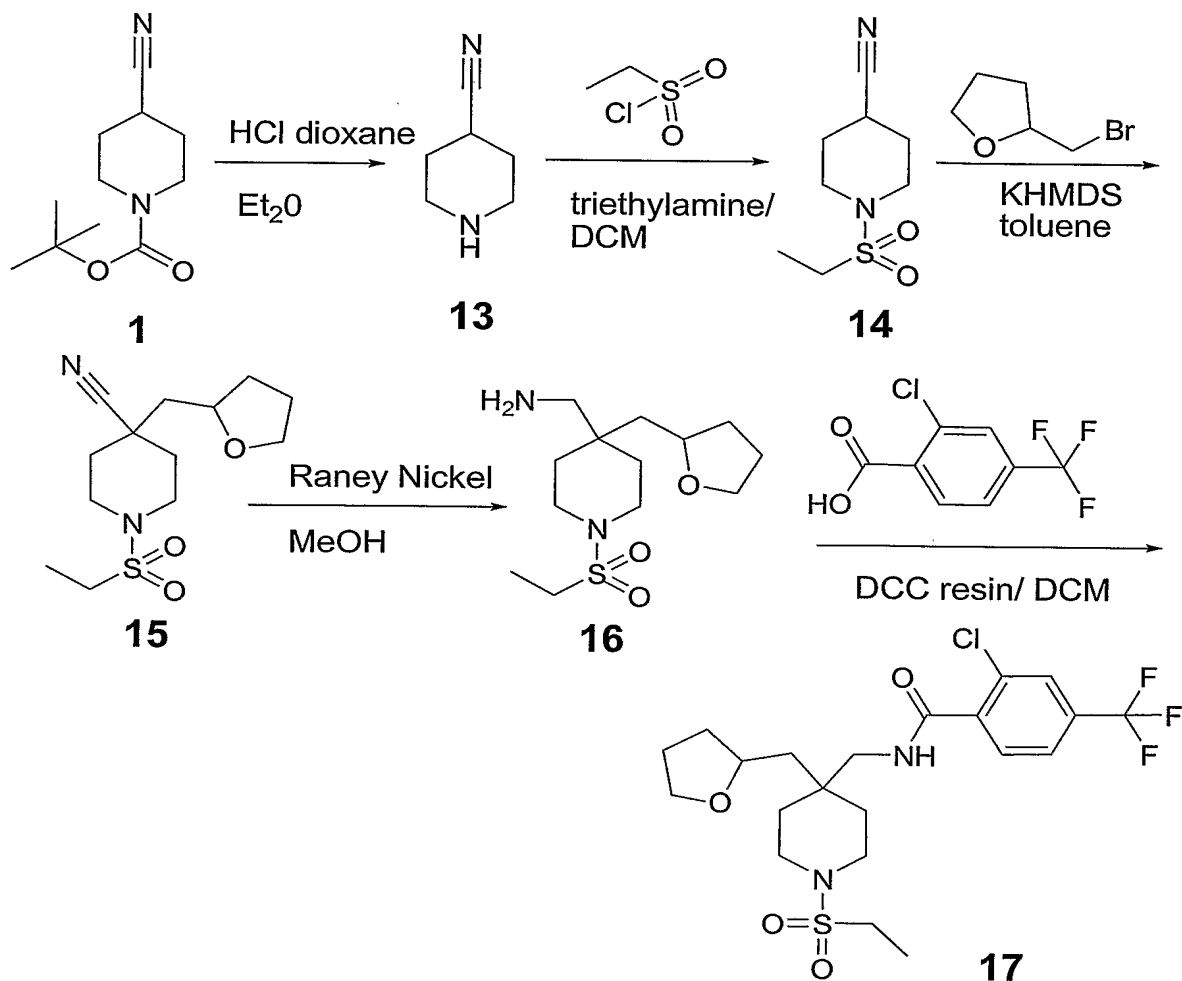
washed with MeOH (200 ml) and the organics were concentrated in vacuo to give 1-[1-(ethylsulfonyl)-4-(tetrahydro-2*H*-pyran-4-ylmethyl)piperidin-4-yl]methanamine (11) as a clear semi-solid. MS 304 (M+1)

2-chloro-*N*-{[1-(ethylsulfonyl)-4-(tetrahydro-2*H*-pyran-4-ylmethyl)piperidin-4-yl]methyl}-4-(trifluoromethyl)benzamide(12)

In a large glass container with a sealable lid was placed 1-[1-(ethylsulfonyl)-4-(tetrahydro-2*H*-pyran-4-ylmethyl)piperidin-4-yl]methanamine (11, 350mg, 1.15 mmol). Dichloromethane (50 ml) and PS-carbodiimide resin (474mg, 2.299 mmol) were added along with 2-chloro-4(trifluoromethyl)benzoic acid (336mg, 1.495 mmol). The lid was sealed and the bottle was shaken for .5 hours. The resin was filtered off and washed with EtOAc (3X 25 ml) and the organics concentrated in vacuo to give an off-white solid. The residue was purified by column chromatography on silica gel, eluting with EtOAc/Hexanes to give 2-chloro-*N*-{[1-(ethylsulfonyl)-4-(tetrahydro-2*H*-pyran-4-ylmethyl)piperidin-4-yl]methyl}-4-(trifluoromethyl)benzamide (12) as a white solid. Calculated HRMS 511.164 Found 511.1649. ¹H NMR (300 MHz D₆DMSO): δ 8.51 (s, 1 H), 7.96 (s, 1 H), 7.80 (d, J =8.1 Hz, 1 H), 7.61 (d, J =7.8 Hz, 1 H), 3.77 (d, J =9.3 Hz, 2 H), 3.41 (s, 2 H), 3.32 (m, 2 H), 3.29 (s, 2 H), 3.21 (s, 4 H), 3.45 (q, J =9 Hz, 2 H), 1.66 (m, 1 H), 1.61 (m, 2 H), 1.564 (s, 2 H), 1.47 (m, 2 H), 1.30 (d, J =4.5 Hz, 2 H), 1.21 (t, J =7.5 Hz, 3 H).

EXAMPLE 12





4-cyanopiperidinium chloride(13)

In a round bottom flask was placed *tert*-butyl 4-cyanopiperidine-1-carboxylate (1) (15g, 71.3 mmol) and diethyl ether (500 ml). To this was added HCl in dioxane (4M, 35.7 ml, 143 mmol) and the solution stirred overnight. A fine white solid was formed in suspension and filtered with a medium frit to give 4-cyanopiperidinium chloride (13) as an HCl salt in quantitative yield after washing with diethyl ether (3X 50 ml). MS 111 (M+1)

1-(ethanesulfonyl)piperidine-4-carbonitrile (14)

In a dry round bottom flask was placed 4-cyanopiperidinium chloride (13, 5g, 45.4 mmol) dichloromethane (150ml) and triethylamine (18.98ml, 136 mmol). To the reaction was added dropwise ethanesulfonyl chloride (4.56 ml, 45.4 mmol) and the solution stirred 1 hour and quenched with water (100 ml). The mixture was extracted with dichloromethane (3x 50 ml) and the combined organic

fractions dried (MgSO₄), filtered, and the solvent evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/Hexanes to give 1-(ethylsulfonyl)piperidine-4-carbonitrile (14) as a white solid. MS 203 (M+1)

5 1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidine-4-carbonitrile(15)

In a dry round bottom flask was placed 1-(ethylsulfonyl)-4-ethynylpiperidine (14) (6.7g, 33.1 mmol) and anhydrous toluene (200 ml). To this was added 2-(bromomethyl)tetrahydrofuran (6.51 ml, 49.7 mmol). Solid KHMDS 1.2 equiv (7.93g, 39.7 mmol) was added in one portion at room temperature and an exotherm was observed. The solution was allowed to stir for 12 hours at which time it was quenched with saturated aq. NH₄Cl solution (100 ml). To the mixture was added EtOAc (50 ml) and the solution was then extracted by dilution with 250 ml, water and 3 washes with EtOAc (75 ml each). The organic layer was washed with brine (200 ml) and dried over MgSO₄. The organic solvent was removed in vacuo to give a yellow solid. . The residue was purified by column chromatography on silica gel, eluting with EtOAc/Hexanes to give 1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidine-4-carbonitrile (15) as a off-white solid. MS 287 (M+1)

15 1-[1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidin-4-yl]methanamine(16)

In a heavy wall flask was placed 1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidine-4-carbonitrile (15, 2g, 6.98 mmol) and 2N ammonia in methanol (50 ml). To this was added commercially available Raney nickel slurry in water (1.8g, 20.94 mmol) and the solution agitated under hydrogen atmosphere (45 psi) at room temp for 12 hours. The catalyst was filtered off using celite and washed with MeOH (200 ml) and the combined organics concentrated in vacuo to give 1-[1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidin-4-yl]methanamine (16) as a clear semi-solid. MS 291 (M+1)

25

2-chloro-N- {[1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidin-4-yl]methyl}-4-(trifluoromethyl)benzamide(17)

In a large glass container with a sealable lid was placed 1-[1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidin-4-yl]methanamine (16, 3.4g, 11.71 mmol), dichloromethane (50 ml) and PS-carbodiimide resin (35.1 mmol) along with 2-chloro-4-(trifluoromethyl)benzoic acid (3.41g, 14.05 mmol). The lid was sealed and the bottle was shaken for .5 hours. The resin was filtered off and washed with EtOAc (3X 25 ml) and the organics concentrated in vacuo to give an off-white solid. The residue was purified by column chromatography on silica gel, eluting with EtOAc/Hexanes to give 2-chloro-N- {[1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidin-4-yl]methyl}-4-

30

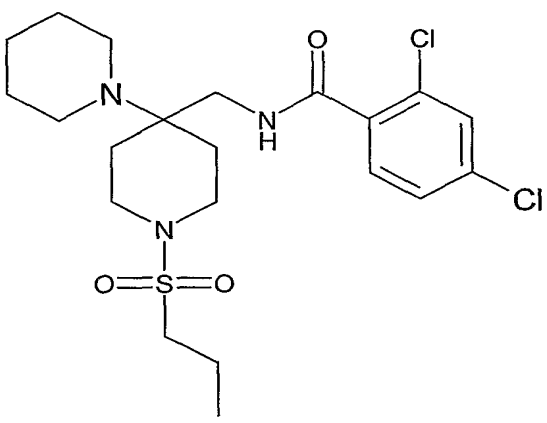
(trifluoromethyl)benzamide (17) as a white solid. Calculated HRMS 497.1483 Found 497.1513. ¹H NMR (300 MHz CDCl₃): δ 7.70 (m, 2 H), 7.59 (d, J = 7.8 Hz, 1 H), 3.86 (m, 3 H), 3.68 (q, J = 5.7 Hz, 1 H), 3.57 (m, 2 H), 3.38 (m, 2 H), 3.16 (dt, J = 10.2 Hz, 1 H), 2.99 (q, J = 7.5 Hz, 2 H), 2.00 (m, 1 H), 1.85 (m, 2 H), 1.57 (m, 7 H), 1.38 (t, 7.8 Hz, 3 H).

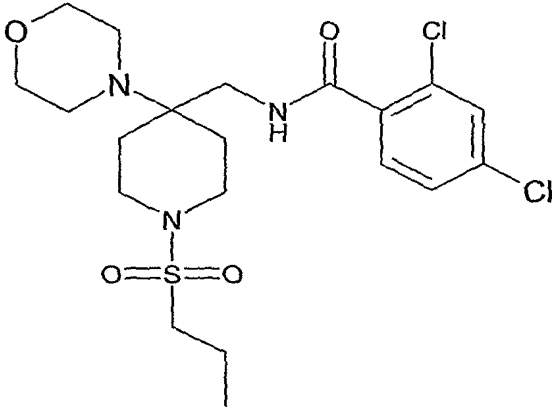
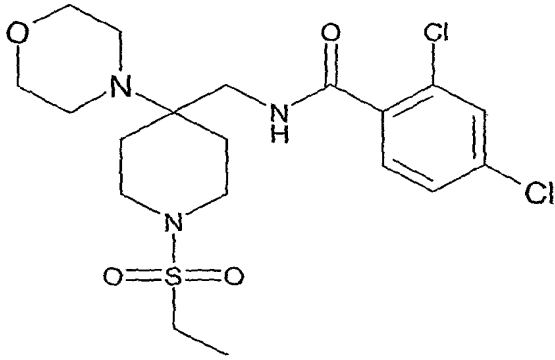
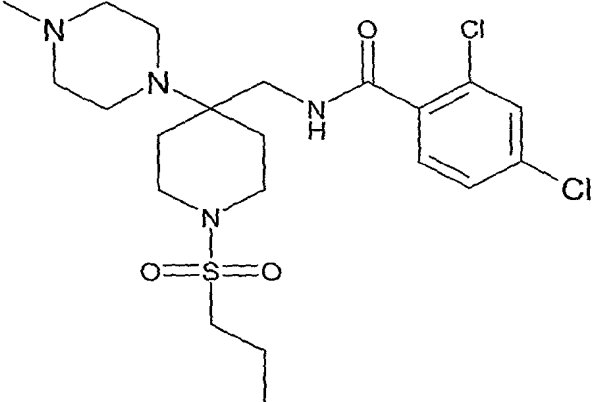
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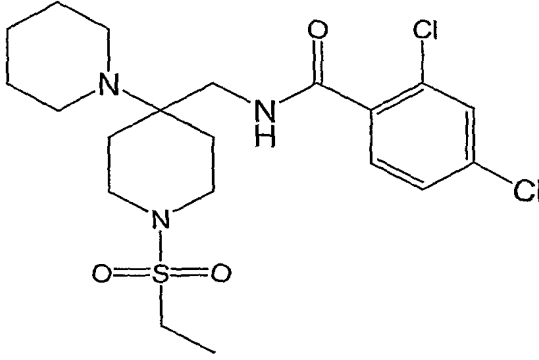
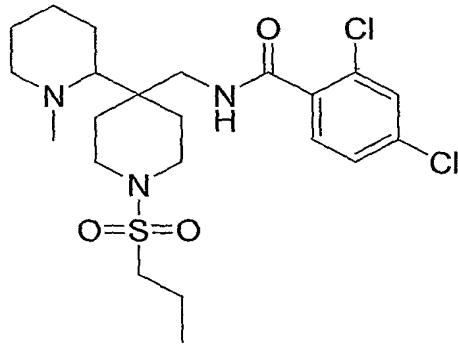
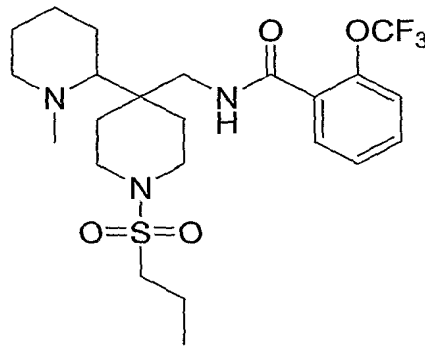
Compounds in Table 1 were synthesized as shown in above, but substituting the appropriately substituted sulfonyl chloride and/or acid chloride/carboxylic acid as described in the Schemes and the foregoing examples. The requisite starting materials were commercially available, described in the literature or readily synthesized by one skilled in the art of organic synthesis.

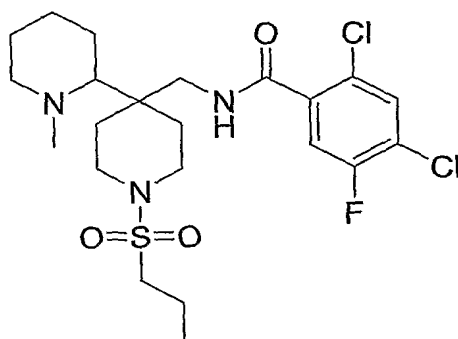
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TABLE 1

Compound	Nomenclature	MS M+1
	2,4-dichloro-N-{[1'-(propylsulfonyl)-1,4'-bipiperidin-4'-yl]methyl}benzamide	477

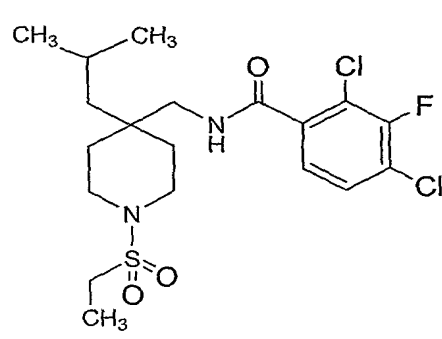
	2,4-dichloro-N-([4-morpholin-4-yl-1-(propylsulfonyl)piperidin-4-yl]methyl)benzamide	479
	2,4-dichloro-N-([1-(ethylsulfonyl)-4-morpholin-4-yl]piperidin-4-yl)methyl)benzamide	465
	2,4-dichloro-N-([4-(4-methylpiperazin-1-yl)-1-(propylsulfonyl)piperidin-4-yl]methyl)benzamide	492

	2,4-dichloro- <i>N</i> -{[1'-(ethylsulfonyl)-1,4'-bipiperidin-4'-yl]methyl}benzamide	462.43
	2,4-dichloro- <i>N</i> -{[1'-(propylsulfonyl)-4'-(1-methyl-piperidin-2-yl)-piperidin-4'-yl]methyl}benzamide	490.5
	2-(trifluoromethoxy)- <i>N</i> -{[1'-(propylsulfonyl)-4'-(1-methyl-piperidin-2-yl)-piperidin-4'-yl]methyl}benzamide	505.6

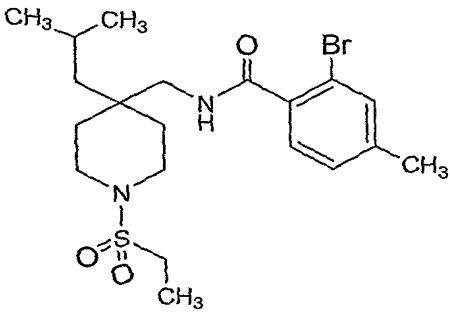
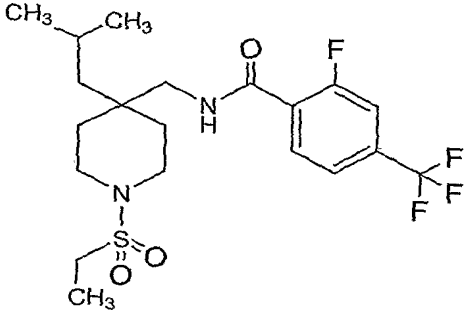
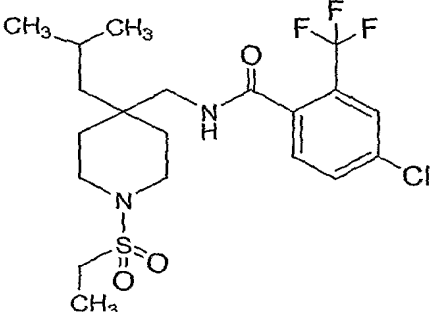
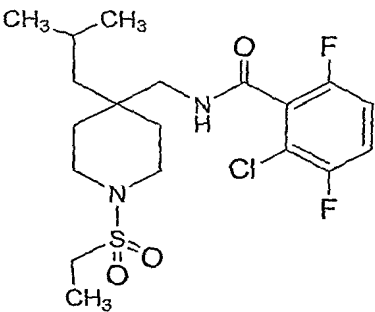
	2,4-dichloro-5-fluoro- <i>N</i> -{[1'-(propylsulfonyl)-4'-(1-methyl-piperidin-2-yl)-piperidin-4'-yl]methyl}benzamide	508.5
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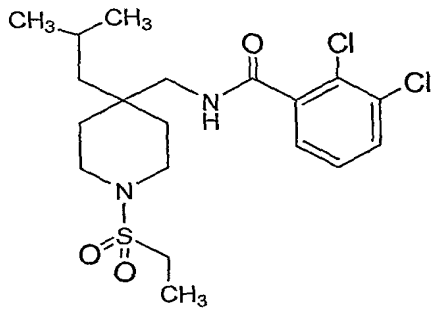
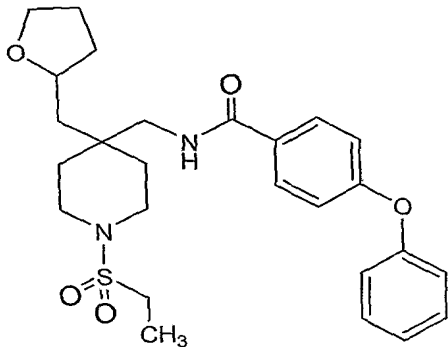
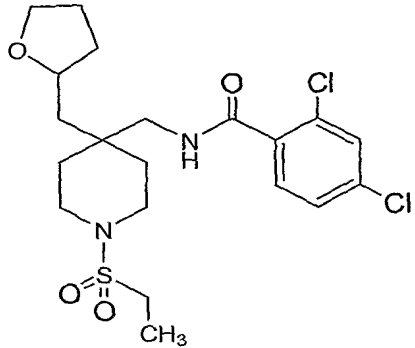
Compounds in Table 2 were synthesized as shown in above, but substituting the appropriately substituted sulfonyl chloride and/or acid chloride/carboxylic acid as described in the Schemes and the foregoing examples. The requisite starting materials were commercially available, described in the literature or readily synthesized by one skilled in the art of organic synthesis.

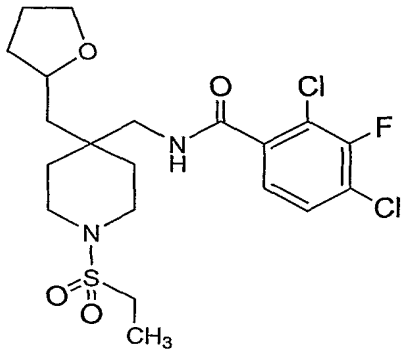
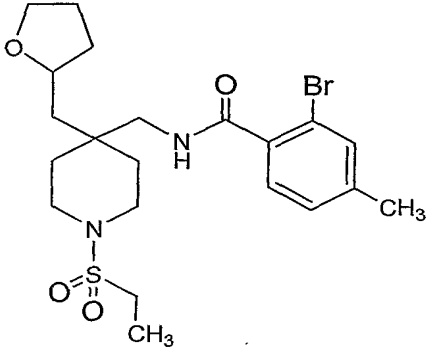
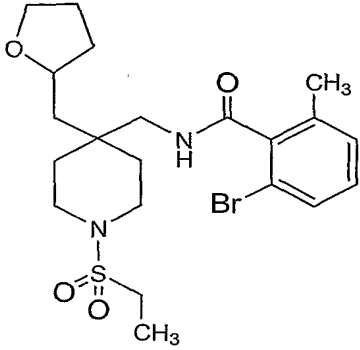
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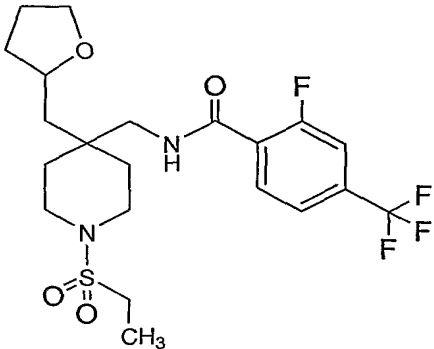
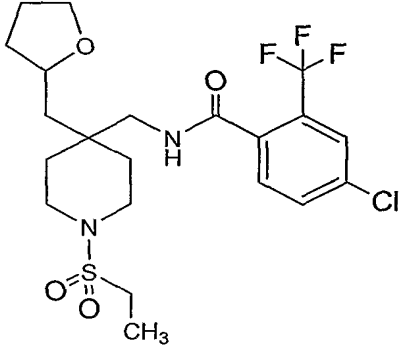
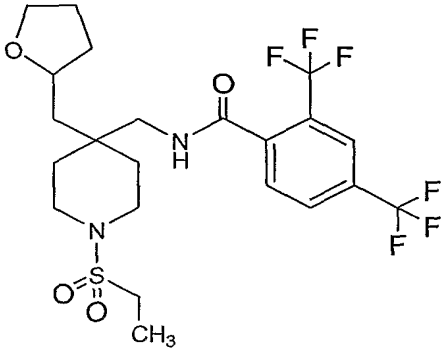
Compound	Nomenclature	MS M+1
	2,4-dichloro- <i>N</i> -{[1-(ethylsulfonyl)-4-isobutylpiperidin-4'-yl]methyl}-3-fluorobenzamide	454

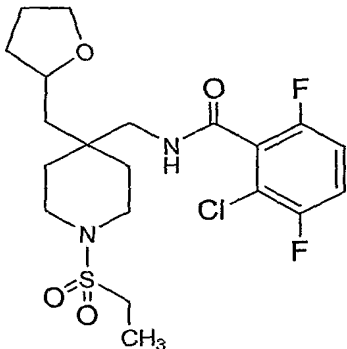
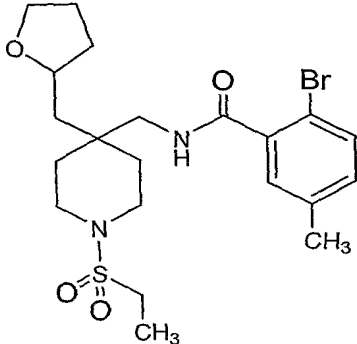
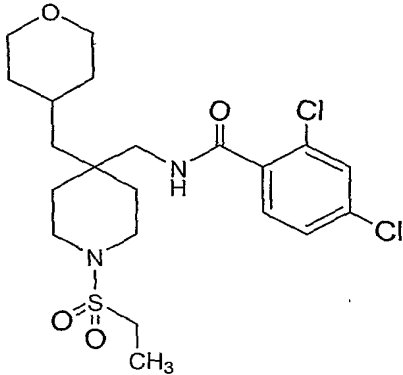
	<i>N</i> -{[1-(ethylsulfonyl)-4-isobutylpiperidin-4-yl]methyl}-4-phenoxybenzamide	459
	2-bromo- <i>N</i> -{[1-(ethylsulfonyl)-4-isobutylpiperidin-4-yl]methyl}-5-methylbenzamide	460
	2-bromo- <i>N</i> -{[1-(ethylsulfonyl)-4-isobutylpiperidin-4-yl]methyl}-6-methylbenzamide	460
	<i>N</i> -{[1-(ethylsulfonyl)-4-isobutylpiperidin-4-yl]methyl}-2,4-bis(trifluoromethyl)benzamide	503

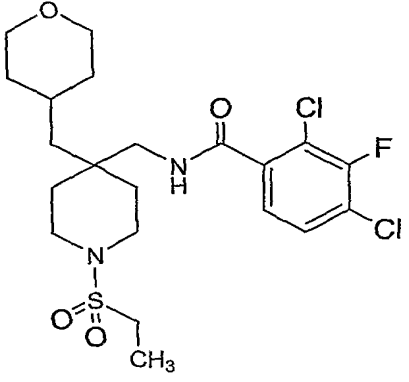
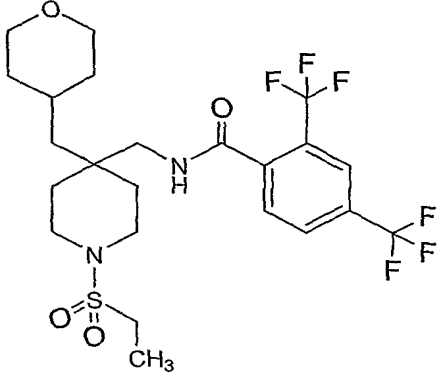
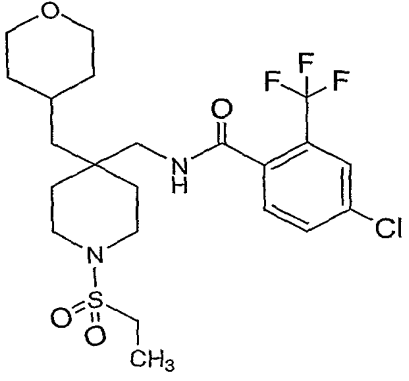
	2-bromo- <i>N</i> -{[1-(ethylsulfonyl)-4-isobutylpiperidin-4-yl]methyl}-4-methylbenzamide	460
	<i>N</i> -{[1-(ethylsulfonyl)-4-isobutylpiperidin-4-yl]methyl}-2-fluoro-4-(trifluoromethyl)benzamide	453
	4-chloro- <i>N</i> -{[1-(ethylsulfonyl)-4-isobutylpiperidin-4-yl]methyl}-2-(trifluoromethyl)benzamide	469
	2-chloro- <i>N</i> -{[1-(ethylsulfonyl)-4-isobutylpiperidin-4-yl]methyl}-3,6-difluorobenzamide	437

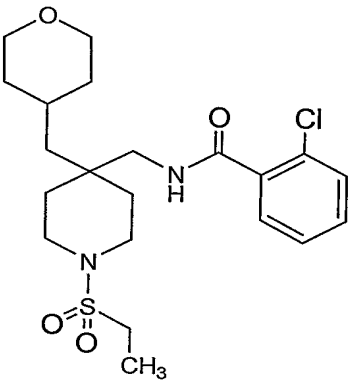
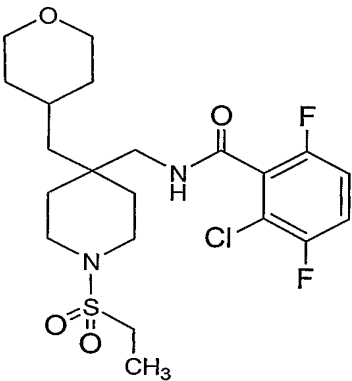
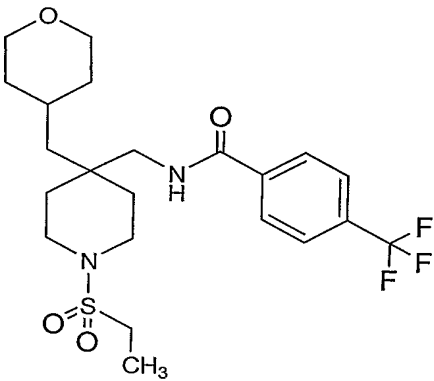
	2,3-dichloro- <i>N</i> -{[1-(ethylsulfonyl)-4-isobutylpiperidin-4-yl]methyl}benzamide	436
	<i>N</i> -{[1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidin-4-yl]methyl}-4-phenoxybenzamide	487
	2,4-dichloro- <i>N</i> -{[1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidin-4-yl]methyl}benzamide	464

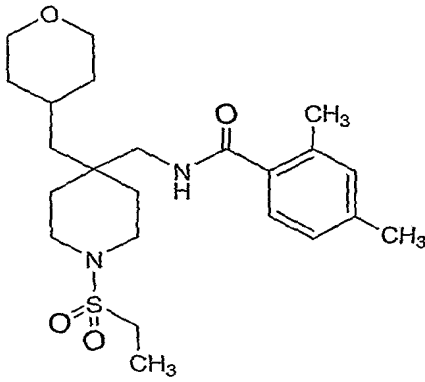
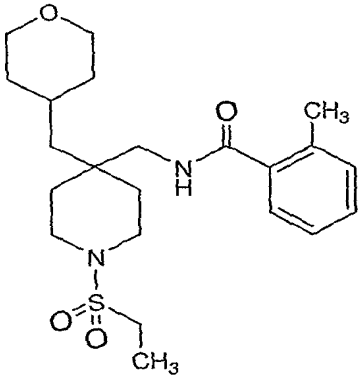
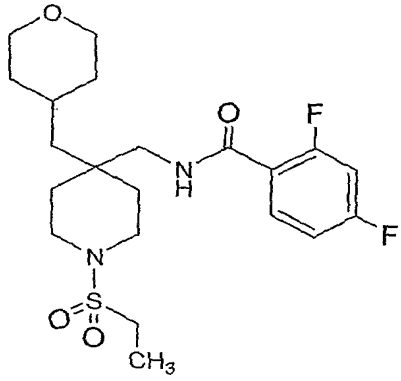
	2,4-dichloro- <i>N</i> -{[1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidin-4-yl]methyl}-3-fluorobenzamide	482
	2-bromo- <i>N</i> -{[1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidin-4-yl]methyl}-4-methylbenzamide	488
	2-bromo- <i>N</i> -{[1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidin-4-yl]methyl}-6-methylbenzamide	488

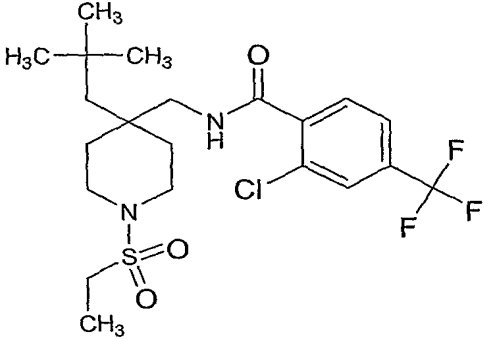
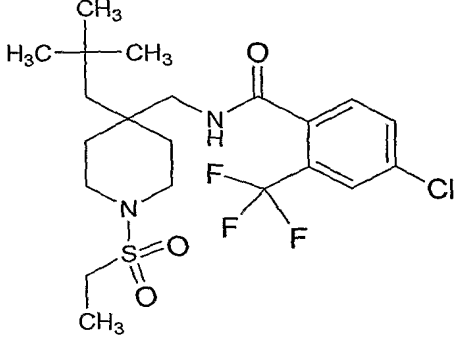
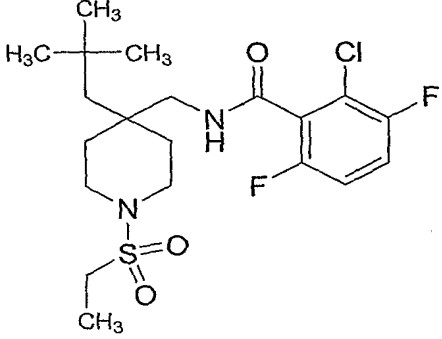
	<i>N</i> -{[1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidin-4-yl]methyl}-2-fluoro-4-(trifluoromethyl)benzamide	481
	4-chloro- <i>N</i> -{[1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidin-4-yl]methyl}-2-(trifluoromethyl)benzamide	497
	<i>N</i> -{[1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidin-4-yl]methyl}-2,4-bis(trifluoromethyl)benzamide	531

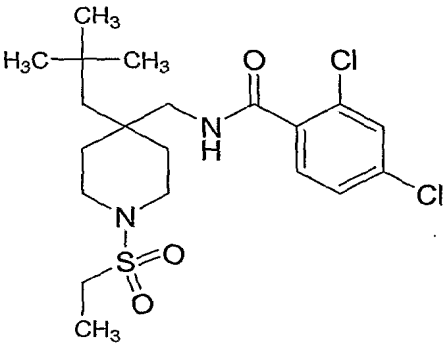
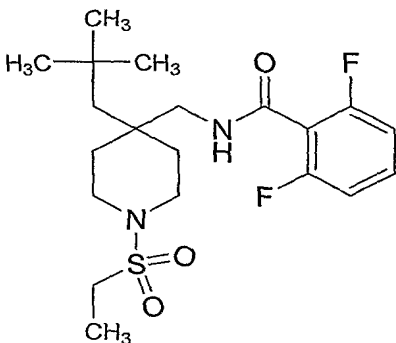
	2-chloro- <i>N</i> -{[1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidin-4-yl]methyl}-3,6-difluorobenzamide	465
	2-bromo- <i>N</i> -{[1-(ethylsulfonyl)-4-(tetrahydrofuran-2-ylmethyl)piperidin-4-yl]methyl}-5-methylbenzamide	488
	2,4-dichloro- <i>N</i> -{[1-(ethylsulfonyl)-4-(tetrahydro-2 <i>H</i> -pyran-4-ylmethyl)piperidin-4-yl]methyl}benzamide	478

	<p>2,4-dichloro-<i>N</i>-{[1-(ethylsulfonyl)-4-(tetrahydro-2<i>H</i>-pyran-4-ylmethyl)piperidin-4-yl]methyl}-3-fluorobenzamide</p>	496
	<p><i>N</i>-{[1-(ethylsulfonyl)-4-(tetrahydro-2<i>H</i>-pyran-4-ylmethyl)piperidin-4-yl]methyl}-2,4-bis(trifluoromethyl)benzamide</p>	545
	<p>4-chloro-<i>N</i>-{[1-(ethylsulfonyl)-4-(tetrahydro-2<i>H</i>-pyran-4-ylmethyl)piperidin-4-yl]methyl}-2-(trifluoromethyl)benzamide</p>	512

	2-chloro- <i>N</i> -{[1-(ethylsulfonyl)-4-(tetrahydro-2 <i>H</i> -pyran-4-ylmethyl)piperidin-4-yl]methyl}benzamide	444
	2-chloro- <i>N</i> -{[1-(ethylsulfonyl)-4-(tetrahydro-2 <i>H</i> -pyran-4-ylmethyl)piperidin-4-yl]methyl}-3,6-difluorobenzamide	479
	<i>N</i> -{[1-(ethylsulfonyl)-4-(tetrahydro-2 <i>H</i> -pyran-4-ylmethyl)piperidin-4-yl]methyl}-4-(trifluoromethyl)benzamide	477

	<i>N</i> -{[1-(ethylsulfonyl)-4-(tetrahydro-2 <i>H</i> -pyran-4-ylmethyl)piperidin-4-yl]methyl}-2,4-dimethylbenzamide	437
	<i>N</i> -{[1-(ethylsulfonyl)-4-(tetrahydro-2 <i>H</i> -pyran-4-ylmethyl)piperidin-4-yl]methyl}-2-methylbenzamide	423
	<i>N</i> -{[1-(ethylsulfonyl)-4-(tetrahydro-2 <i>H</i> -pyran-4-ylmethyl)piperidin-4-yl]methyl}-2,4-difluorobenzamide	445

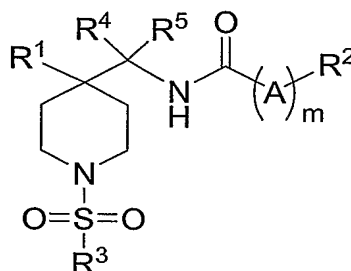
	2-chloro-N-([4-(2,2-dimethylpropyl)-1-(ethylsulfonyl)piperidin-4-yl]methyl)-4-(trifluoromethyl)benzamide	484.0
	4-chloro-N-([4-(2,2-dimethylpropyl)-1-(ethylsulfonyl)piperidin-4-yl]methyl)-2-(trifluoromethyl)benzamide	484.0
	2-chloro-N-([4-(2,2-dimethylpropyl)-1-(ethylsulfonyl)piperidin-4-yl]methyl)-3,6-difluorobenzamide	452.0

	2,4-dichloro-N-{{4-(2,2-dimethylpropyl)-1-(ethylsulfonyl)piperidin-4-yl}methyl}benzamide	450.4
	N-{{4-(2,2-dimethylpropyl)-1-(ethylsulfonyl)piperidin-4-yl}methyl}-2,6-difluorobenzamide	417.5

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A compound of the formula I:



wherein:

R^1 is $-(CH_2)_n-R^{1a}$, wherein n is independently 0-6, and R^{1a} is selected from the group consisting of:

- (1) C_{1-6} alkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxy, phenyl substituted with R^{2a} , R^{2b} and R^{2c} , or heterocycle substituted with R^{2a} , R^{2b} and R^{2c} ,
- (2) C_{3-6} cycloalkyl, which is unsubstituted or substituted with C_{1-6} alkyl, 1-6 halogen, hydroxy or $-NR^{10}R^{11}$,
- (3) piperidiny, which is unsubstituted or substituted with C_{1-6} alkyl, 1-6 halogen, hydroxy, $-O-C_{1-6}$ alkyl, or $-NR^{10}R^{11}$,
- (4) piperaziny, which is unsubstituted or substituted with C_{1-6} alkyl, 1-6 halogen, hydroxy, $-O-C_{1-6}$ alkyl, or $-NR^{10}R^{11}$,
- (5) tetrahydropyrany or tetrahydrofurany, which is unsubstituted or substituted with C_{1-6} alkyl, 1-6 halogen, hydroxy, $-O-C_{1-6}$ alkyl, or $-NR^{10}R^{11}$,
- (6) morpholiny, which is unsubstituted or substituted with C_{1-6} alkyl, 1-6 halogen, hydroxy, $-O-C_{1-6}$ alkyl, or $-NR^{10}R^{11}$,
- (7) $-O-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxy or $-NR^{10}R^{11}$,
- (8) $-CO_2R^9$,

wherein R^9 is independently selected from:

- (a) hydrogen,
- (b) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 fluoro,
- (c) benzyl, and
- (d) phenyl,
- (9) $-NR^{10}R^{11}$,

wherein R^{10} and R^{11} are independently selected from:

- (a) hydrogen,
- (b) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with hydroxy, 1-6 fluoro or $-NR^{12}R^{13}$, where R^{12} and R^{13} are independently selected from hydrogen and $-C_{1-6}$ alkyl,
- (c) $-C_{3-6}$ cycloalkyl, which is unsubstituted or substituted with hydroxy, 1-6 fluoro or $-NR^{12}R^{13}$,
- (d) benzyl,
- (e) phenyl, and
- (10) $-CONR^{10}R^{11}$;

R^2 is selected from the group consisting of:

- (1) phenyl, which is substituted with R^{2a} , R^{2b} and R^{2c} ,
- (2) heterocycle, which is substituted with R^{2a} , R^{2b} and R^{2c} ,
- (3) C_{1-8} alkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxy, $-NR^{10}R^{11}$, phenyl or heterocycle, where the phenyl or heterocycle is substituted with R^{2a} , R^{2b} and R^{2c} ,
- (4) C_{3-6} cycloalkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxy or $-NR^{10}R^{11}$, and
- (5) $-C_{1-6}$ alkyl- $(C_{3-6}$ cycloalkyl), which is unsubstituted or substituted with 1-6 halogen, hydroxy or $-NR^{10}R^{11}$;

R^{2a} , R^{2b} and R^{2c} are independently selected from the group consisting of:

- (1) hydrogen,
- (2) halogen,
- (3) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with:
 - (a) 1-6 halogen,
 - (b) phenyl,
 - (c) C_{3-6} cycloalkyl, or
 - (d) $-NR^{10}R^{11}$,
- (4) $-O-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 halogen,
- (5) $-O$ -phenyl,
- (6) hydroxy,
- (7) $-SCF_3$,
- (8) $-SCHF_2$,
- (9) $-SCH_3$,

- (10) $-\text{CO}_2\text{R}^9$,
(11) $-\text{CN}$,
(12) $-\text{SO}_2\text{R}^9$,
(13) $-\text{SO}_2-\text{NR}^{10}\text{R}^{11}$,
5 (14) $-\text{NR}^{10}\text{R}^{11}$,
(15) $-\text{CONR}^{10}\text{R}^{11}$, and
(16) $-\text{NO}_2$;

R^3 is selected from the group consisting of:

- (1) C_{1-6} alkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxyl,
10 $-\text{NR}^{10}\text{R}^{11}$,
(2) C_{3-6} cycloalkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxyl or
 $-\text{NR}^{10}\text{R}^{11}$,
(3) $-\text{C}_{1-6}$ alkyl- $(\text{C}_{3-6}$ cycloalkyl), which is unsubstituted or substituted with 1-6 halogen,
hydroxy or $-\text{NR}^{10}\text{R}^{11}$, and
15 (4) $-\text{NR}^{10}\text{R}^{11}$;

with the proviso that if R^1 is $-\text{CH}_2$ -cyclopropyl, then R^3 is $-\text{NR}^{10}\text{R}^{11}$ or

$-\text{C}_{1-6}$ alkyl- $(\text{C}_{3-6}$ cycloalkyl), which is unsubstituted or substituted with 1-6 halogen,
hydroxy or $-\text{NR}^{10}\text{R}^{11}$;

R^4 and R^5 are independently selected from the group consisting of:

- (1) hydrogen, and
20 (2) C_{1-6} alkyl, which is unsubstituted or substituted with halogen or hydroxyl,
or R^4 and R^5 taken together form a C_{3-6} cycloalkyl ring;

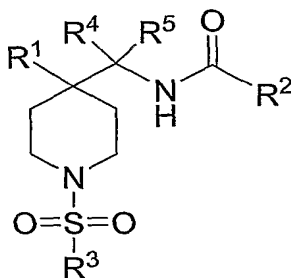
A is selected from the group consisting of:

- (1) $-\text{O}-$, and
25 (2) $-\text{NR}^{10}-$;

m is zero or one, whereby when m is zero, R^2 is attached directly to the carbonyl;

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

2. The compound of Claim 1 of the formula



Ic

or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 1 wherein R^1 is $-(CH_2)_n-R^{1a}$, wherein n is independently 0-6, and R^{1a} is selected from the group consisting of:

- (1) C₃-6cycloalkyl, which is unsubstituted or substituted with C₁-6alkyl, 1-6 halogen, or hydroxy.
- (2) piperidinyl, which is unsubstituted or substituted with C₁-6alkyl, 1-6 halogen, hydroxy, or -O-C₁-6alkyl,
- (3) piperazinyl, which is unsubstituted or substituted with C₁-6alkyl, 1-6 halogen, hydroxy, or -O-C₁-6alkyl,
- (4) tetrahydropyranyl, which is unsubstituted or substituted with C₁-6alkyl, 1-6 halogen, hydroxy, or -O-C₁-6alkyl, and
- (5) morpholinyl, which is unsubstituted or substituted with C₁-6alkyl, 1-6 halogen, hydroxy, or -O-C₁-6alkyl.

4. The compound of Claim 3 wherein R^1 is selected from the group consisting of:

- (1) -CH₂-cyclopropyl,
- (2) piperidinyl,
- (3) N-methyl-piperidinyl,
- (4) N-methyl-piperazinyl, and
- (5) morpholinyl.

5. The compound of Claim 1 wherein R^4 is C₁-3alkyl and R^5 is hydrogen or C₁-3alkyl.

6. The compound of Claim 5 wherein R⁴ is C₁₋₃alkyl in the (S) configuration and R⁵ is hydrogen.

7. The compound of Claim 1 wherein R⁴ is hydrogen and R⁵ is hydrogen.

8. The compound of Claim 1 wherein R² is selected from the group consisting of:

- (1) phenyl, which is substituted with R^{2a}, R^{2b} and R^{2c},
- (2) thienyl, which is substituted with R^{2a}, R^{2b} and R^{2c},
- (3) C₁₋₆alkyl, which is unsubstituted or substituted with 1-6 halogen, phenyl or -NR¹⁰R¹¹, where the phenyl is substituted with R^{2a}, R^{2b} and R^{2c},
- (4) C₃₋₆cycloalkyl, which is unsubstituted or substituted with 1-6 halogen, hydroxy or -NR¹⁰R¹¹, and

R^{2a}, R^{2b} and R^{2c} are independently selected from the group consisting of:

- (1) hydrogen,
- (2) halogen,
- (3) -C₁₋₆alkyl,
- (4) -O-C₁₋₆alkyl,
- (5) -CF₃,
- (6) -OCF₃,
- (7) -OCHF₂,
- (8) -SCF₃,
- (9) -SCHF₂, and
- (10) -NH₂.

9. The compound of Claim 8 wherein R² is phenyl or thienyl and R^{2a}, R^{2b} and R^{2c} are independently selected from the group consisting of:

- (1) hydrogen,
- (2) halogen,
- (3) -C₁₋₆alkyl,
- (4) -O-C₁₋₆alkyl,
- (5) -CF₃,
- (6) -OCF₃,
- (7) -OCHF₂,
- (8) -SCF₃,

- (9) -SCHF₂, and
- (10) -NH₂.

10. The compound of Claim 9 wherein R² is phenyl and R^{2a}, R^{2b} and R^{2c} are
5 independently selected from the group consisting of:

- (1) hydrogen,
- (2) fluoro,
- (3) chloro,
- (4) bromo,
- 10 (5) -OCH₃,
- (6) -CF₃, and
- (7) -NH₂.

11. The compound of Claim 10 wherein R² is phenyl and R^{2a}, R^{2b} and R^{2c} are
15 independently selected from the group consisting of:

- (1) hydrogen,
- (2) fluoro,
- (3) chloro, and
- 20 (4) bromo.

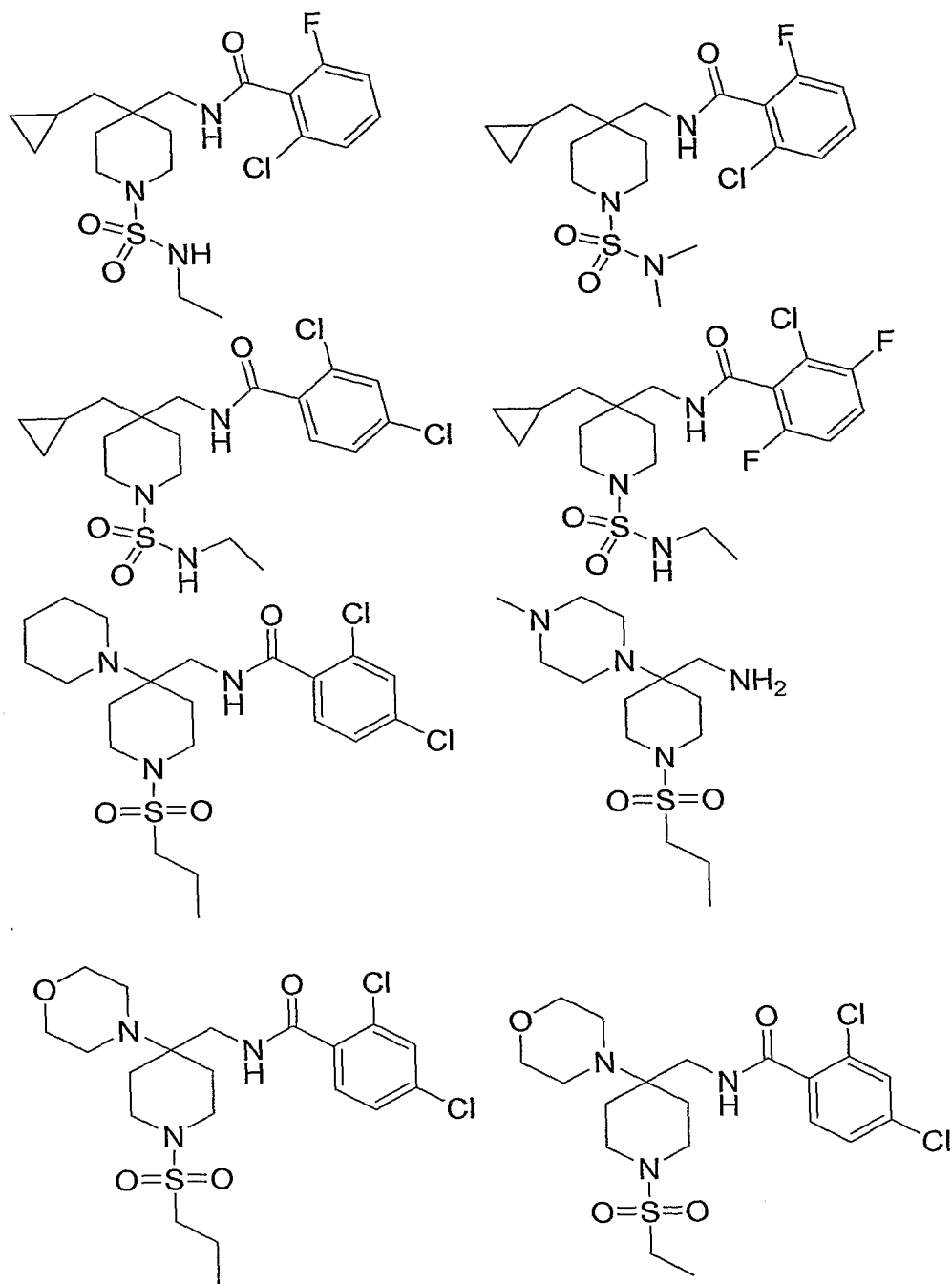
12. The compound of Claim 11 wherein R² is 2,4-dichlorophenyl.

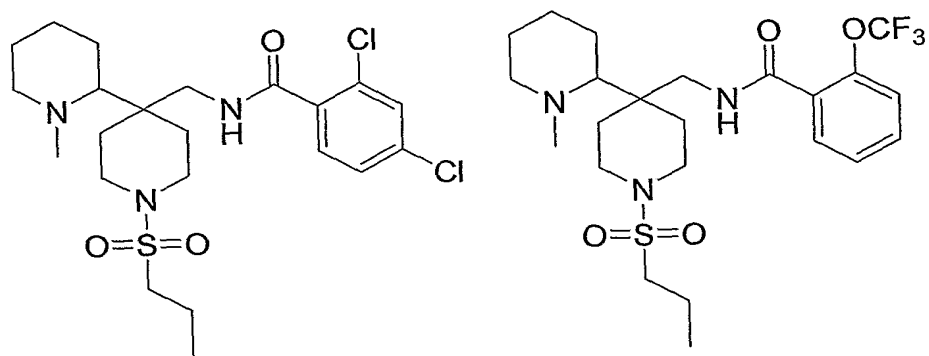
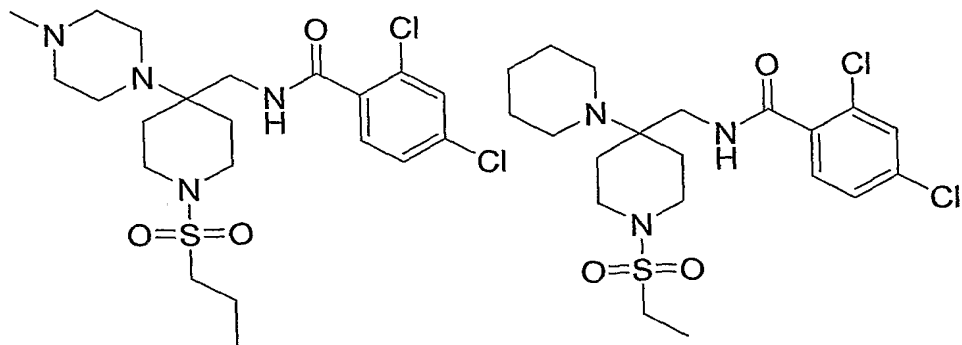
13. The compound of Claim 1 wherein R³ is selected from the group consisting of:

- (1) -NH(C₁-6alkyl);
- 25 (2) -N(C₁-6alkyl)₂;
- (3) C₁-6alkyl, which is unsubstituted or substituted with fluoro, C₃-6cycloalkyl, C₁-6alkyl-cyclopropyl, -NH(C₁-6alkyl), -N(C₁-6alkyl)(C₁-6alkyl) or azediny, which is unsubstituted or substituted with fluoro.

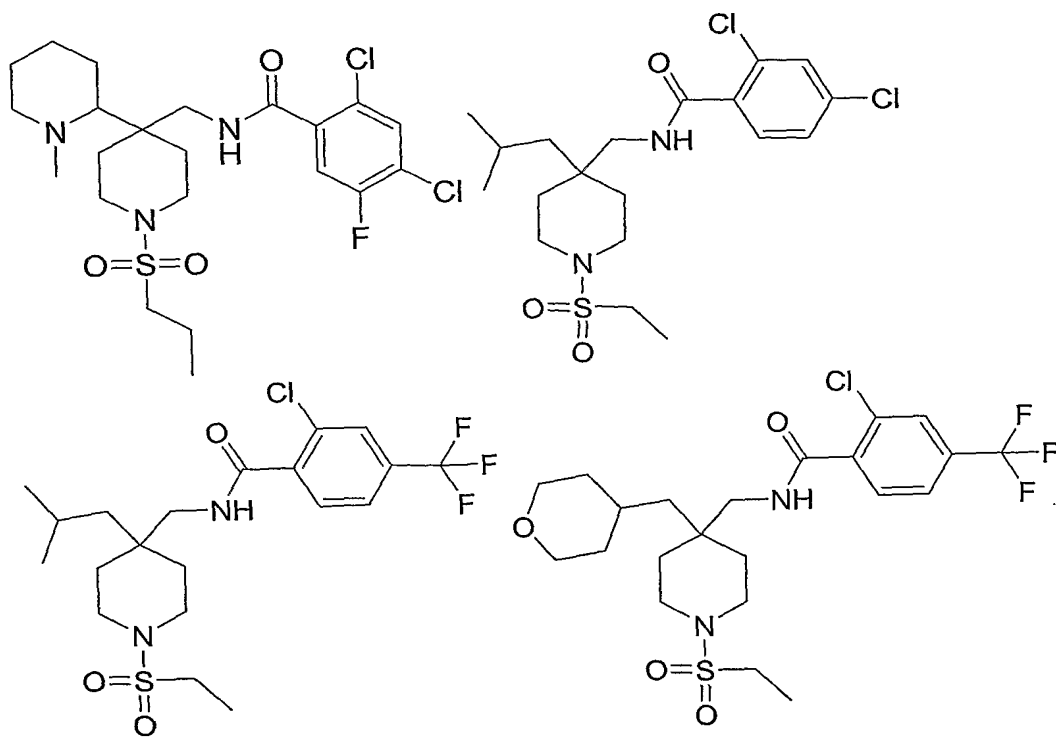
14. The compound of Claim 13 wherein R³ is selected from the group consisting of:
30 -NHCH₂CH₃, -N(CH₃)₂, -CH₂CH₃, -CH₂CH₂F, -(CH₂)₂CH₃, cyclopropyl, and -CH₂cyclopropyl.

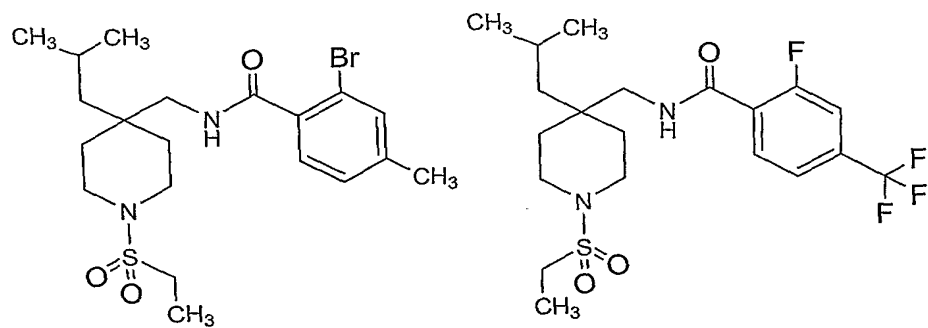
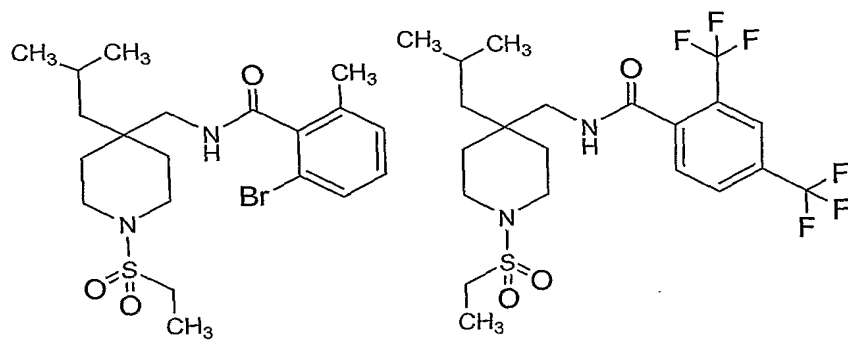
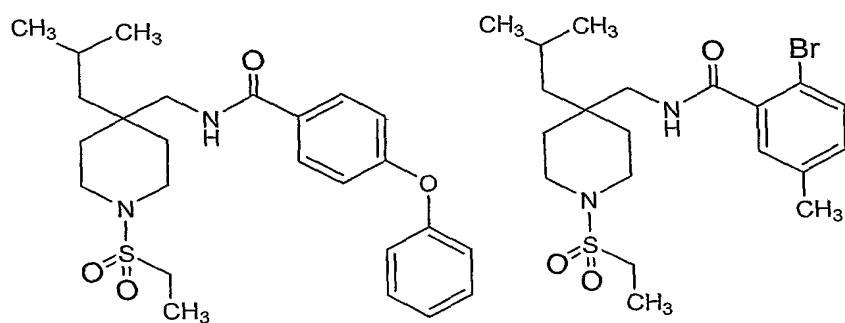
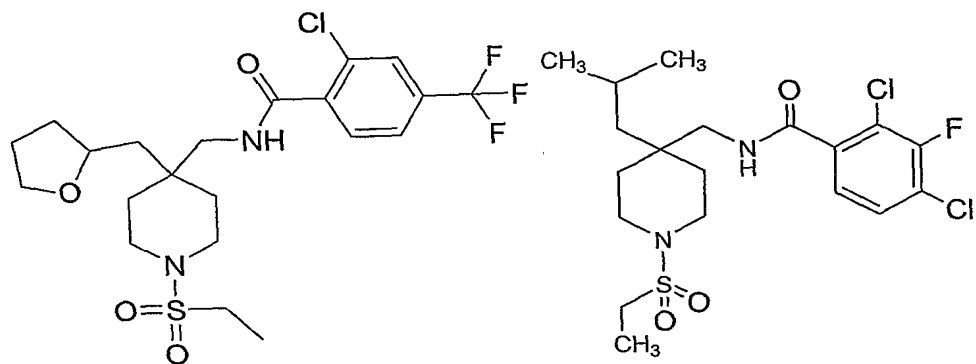
15. A compound which is selected from the group consisting of:

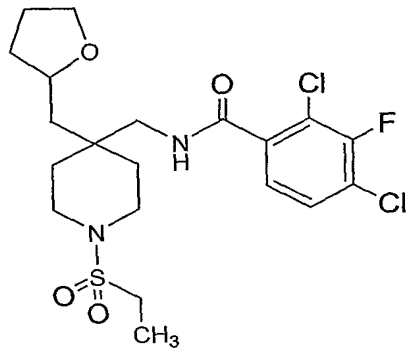
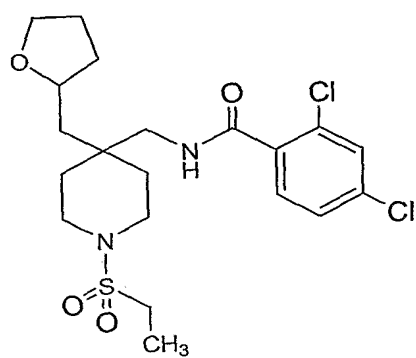
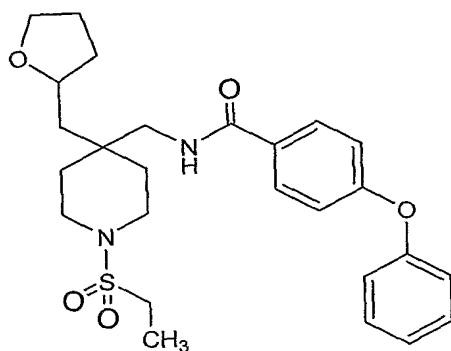
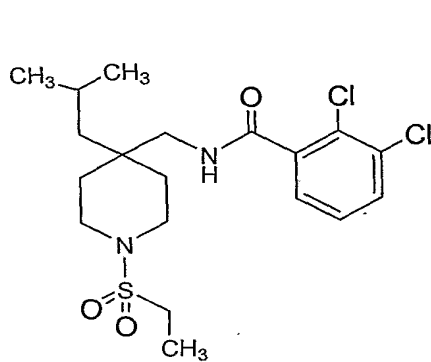
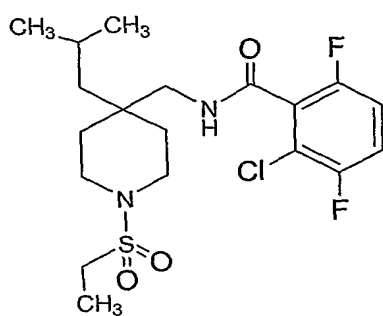
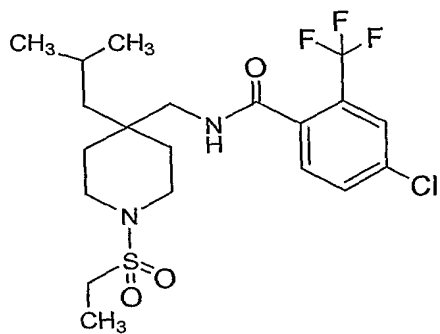


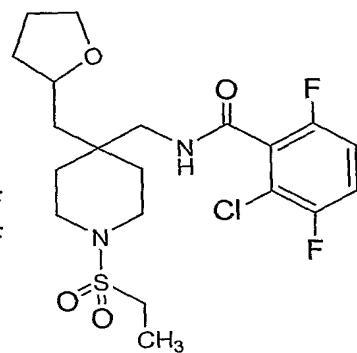
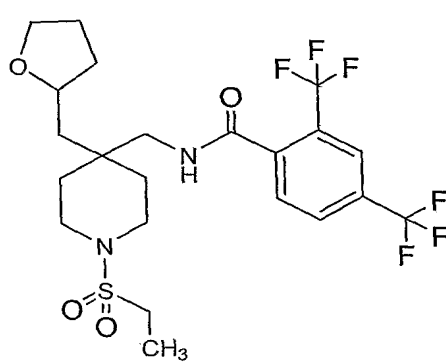
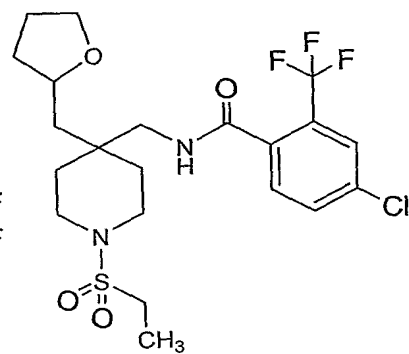
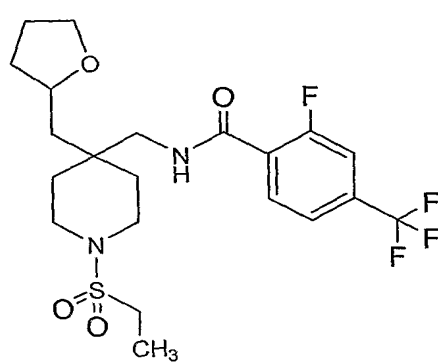
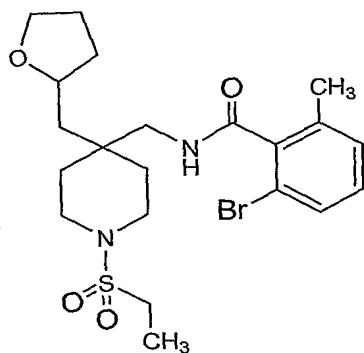
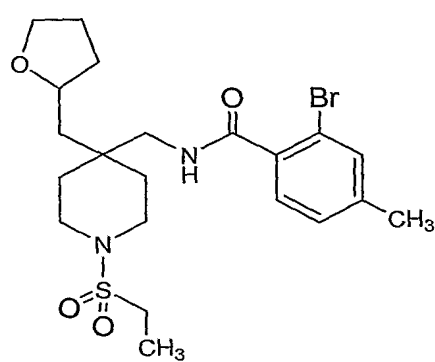


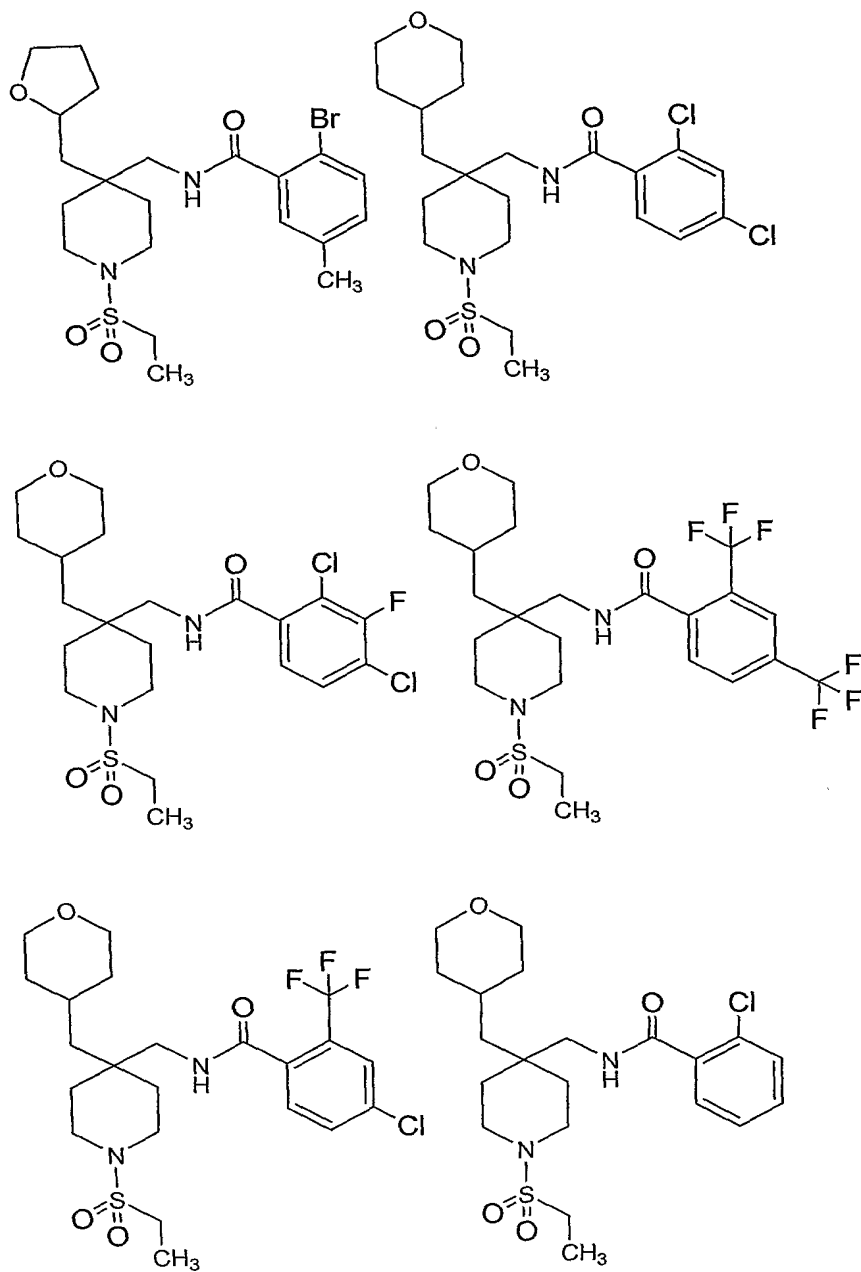
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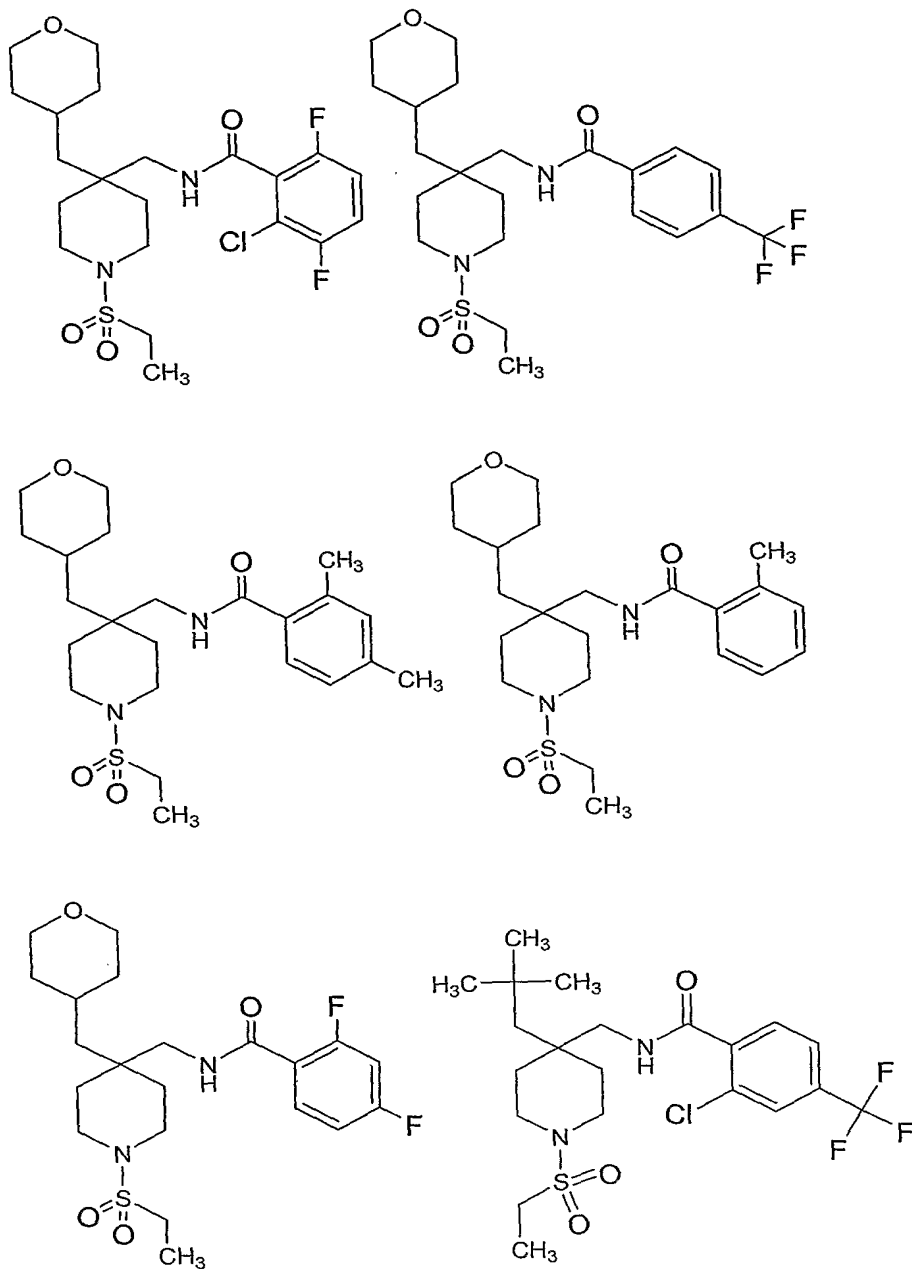


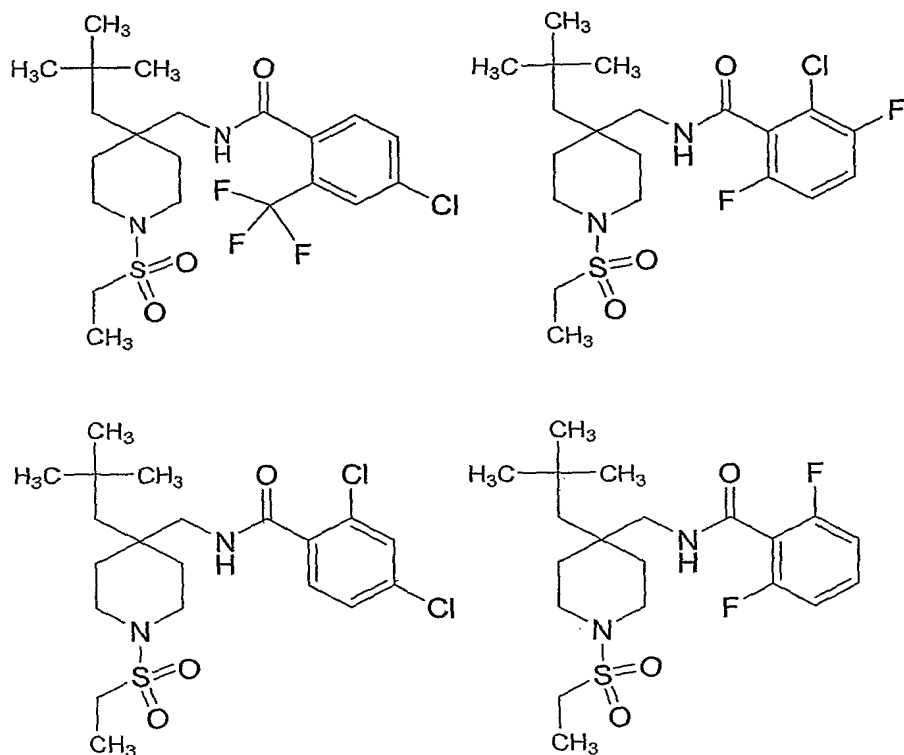












or a pharmaceutically acceptable salt thereof.

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16. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a compound of Claim 1 or a pharmaceutically acceptable salt thereof.

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17. A method for inhibiting the glycine transporter GlyT1 in a mammal in need thereof which comprises the administration of an effective amount of the compound of Claim 1 or a pharmaceutically acceptable salt thereof.

15

18. A method for the manufacture of a medicament for inhibiting the glycine transporter GlyT1 in a mammal in need thereof comprising combining the compound of Claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutical carrier or diluent.

19. A method for treating a neurological and psychiatric disorders associated with glycinergic or glutamatergic neurotransmission dysfunction in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1 or a pharmaceutically acceptable salt thereof.

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20. A method for treating schizophrenia in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1 or a pharmaceutically acceptable salt thereof.